

THE PARATHYROID GLANDS
AND
METABOLIC BONE DISEASE
SELECTED STUDIES

THE PARATHYROID GLANDS AND METABOLIC BONE DISEASE

SELECTED STUDIES

BY

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PREFACE AND CRITICAL REVIEW COMBINED

On starting to write the preface it occurred to the authors that it might be well to incorporate their own critical review. The thought existed it must be admitted that by pointing out the shortcomings in particular the wind might be taken out of the sails of those of the reviewers who will be impressed largely by the faults of this work. In other words we are incorporating a little prophylactic criticism.

What is meant by the last two words in the title. *Selected Studies*? What studies were selected? Were they selected in order that the final presentation might be a systematic covering of the entire field? Were they selected for clinical importance? No they were selected because the authors had had some first hand experience with them and felt that they might have something to contribute. To this fact are to be attributed largely the many glaring mistakes on the one hand the over emphasis of certain other features on the other hand.

Where one of the selected studies had previously been published the authors did not hesitate to incorporate large sections of it almost verbatim they attempted with every section however to bring it up to date and to integrate it closely with the new data.

For those who are not familiar with previous publications from our group it might be stated that we are not content merely to present data we attempt where possible to develop an hypothesis upon which to hang the observations. The hypotheses—it almost follows—are subject to change without notice.

The authors are aware of some of the liberties they have taken with the English language. They have used many medical colloquialisms. They have followed the current vogue in medical writing of using nouns for adjectives. It is more convenient if not such good English to use the expression serum phosphorus instead of level of phosphorus in the serum. The German language by running several nouns together into one word can cope with the difficulty more simply and accurately, it would employ the expression *Serumphosphorgehalt*.

In a way, this work represents an incomplete summary of studies on calcium metabolism carried out on the Metabolic Ward (Ward 4) of the Massachusetts General Hospital over a period of 24 years. Researchers have come and researchers have gone but the studies on calcium metabolism have continued uninterruptedly. Indeed neither of the present authors was a charter member of this group of metabolic investigators credit for the initial impetus belongs to Dr. Joseph C. Aub and his associates for their now classical studies on lead poisoning [Aub, Fairhall Minot, and Reznikoff (1925)]

The studies here selected have been carried out with the help of a large number of collaborators, most of whom appear at one time or another as joint authors of our previously published reports. The more recent work which has not been published has been carried out in conjunction with Dr Frederic C Bartter, Dr Charles H Burnett, Dr Russell W Fraser, Dr Anne P Forbes, Dr Laurance W Kinsell, Dr Harry F Klinefelter, Jr, Dr William Parson, Dr Patricia Smith Benedict, and Dr Hersh W Sulkowitch. To these names must be added those of Evelyn Carroll, Lowell D Cox, Eleanor F Dempsey, Elizabeth C Donaldson, Esther Bloomberg Gordon, Grace C Griswold, Priscilla White Lindsay, Marian MacAulay, Dorothy Bryant Nodine, Robin M Suby, and Shirley L Wells, to whom we are grateful for technical assistance.

Of the good and hitherto unpublished observations contained in this book, many stem from that eminent pathologist, the late Professor Jacob Erdheim of Vienna, at whose elbow during the year of 1930 one of us (F A) had the good fortune of standing and picking up the pearls. We were pleased to note that Dr Joseph P Weinmann and Dr Harry Sicher, in their recently published excellent book entitled, "Bone and Bones" [The C V Mosby Company (1947)], dedicated their work to this renowned Viennese investigator. Professor Erdheim made many fundamental observations on the pathology and functions of the parathyroid glands and on various forms of bone disease, to him belongs the credit for first connecting the parathyroids with calcium metabolism when in 1906, he showed that parathyroidectomy resulted in a calcification of the dentine of rats' teeth.

A number of professional colleagues in the Massachusetts General Hospital and elsewhere have generously assisted in many ways in the studies herein reported. Although it is impossible to name all of these individuals, we want to thank all of them, and especially those listed below.

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Boston, Massachusetts
New York, New York

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CHAPTER 1

THE PARATHYROID GLANDS NORMAL AND PATHOLOGIC PHYSIOLOGY

In the final analysis very little is known about anything and much that seems true today turns out to be only partly true tomorrow but as things go in medicine our knowledge of the interrelation one to another of all the sequelae which result from the action of the parathyroid hormone is probably clearer than that for any other hormone The authors have found it convenient to make some crude diagrams of the important structures and substances affected by the hormone The reader however is cautioned against taking these diagrams too literally

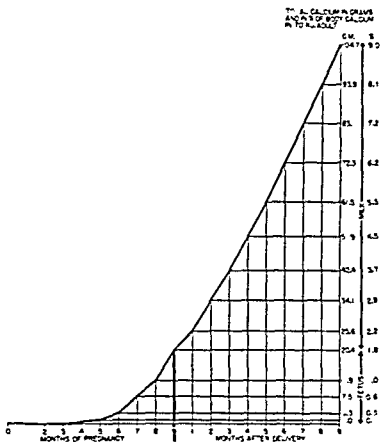
It will be desirable first to consider the calcium and phosphorus metabolism in the normal or isoparathyroid state in the adult before proceeding to the hypo- and hyperparathyroid states

I ISOPARATHYROIDISM

The normal serum calcium value is 10.0 mg per 100 cc plus or minus one milligram At this level a considerable amount of calcium is excreted in the urine so that on a calcium intake of 0.05 gm there is a constant drain of calcium from the body The threshold for calcium excretion in the urine is about 7.0 mg per 100 cc Calcium is apparently also excreted into the gastrointestinal tract since on a very low calcium intake the fecal excretion may be greater than the intake Other sources of calcium loss are the lactating breast (one quart of human milk contains *circa* 400 mg of calcium) and the placenta The latter becomes a source of appreciable calcium loss only during the last two months of pregnancy Fig 1 shows the relative unimportance of pregnancy as a cause of calcium depletion in the mother and the far greater drain of calcium from the mother during lactation Since over ninety nine per cent of the body calcium is contained in the bones or teeth it follows that if the calcium output from the above mentioned exits is greater than the calcium intake the deficit will have to come from the bones (or teeth)

Whereas in the skeleton bone is constantly being laid down and resorbed (*vide infra*) there is no such turnover of tissue in the teeth It may be that there is a very slight interchange of calcium in the adult tooth but for all practical purposes this may be disregarded When the tooth is being laid down there can be a calcification if the calcium metabolism of the body is faulty, once the tooth is formed however, there is no decalcification This principle is well illustrated by the teeth of adult rats

The incisor teeth of the rat are constantly being worn off from without and renewed from within the back teeth on the other hand are formed once and for all like human teeth. If one puts an adult rat on a deficiency regimen of the right sort one can produce *osteodystrophia* of the new dentine being laid down in the incisor teeth but the back teeth remain normal.



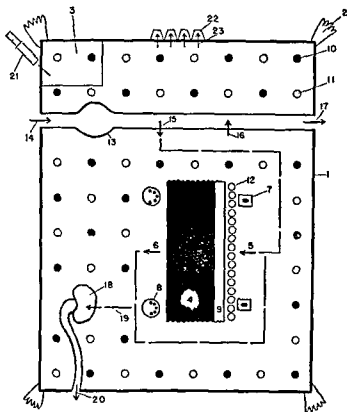


Fig. 2 Diagrammatic Representation of Calcium Metabolism in Isoparathyroid State to be Compared with Similar Diagrams for Hyperparathyroidism With Bone Disease (Fig. 10), Hyperparathyroidism Without Bone Disease (Fig. 11), and Hypoparathyroidism (Fig. 9)

1—confines of body, 2—rudimentary appendages to make body more realistic 3—special compartment of body fluids to represent serum, 4—rectangular mass representing calcified bone and having two surfaces one to the left where bone is being resorbed and one to the right where bone is being formed 5—arrow indicating rate of calcium deposition into bone forming surface, 6—arrow indicating rate of bone resorption from bone resorbing surfaces, 7—osteoblasts laying down uncalcified matrix (9) on bone forming surfaces, 8—osteoclasts on bone resorbing surface, 9—uncalcified osteoid tissue laid down by osteoblasts, 10—black dots representing calcium ions in body fluids, 11—white dots representing phosphate ions in body fluids, 12—localized increase of phosphate ions along bone depositing surfaces resulting from action of phosphatase, 13—gastro intestinal tract, 14—calcium entering the body in the food, 15—calcium being absorbed from the gastro intestinal tract, 16—calcium being re excreted into the gastro intestinal tract, 17—calcium being lost in the feces, 18—kidneys, 19—calcium passing through the kidneys prior to excretion, 20—calcium being lost in the urine, 21—syringe obtaining serum for analysis, 22—tooth, 23—calcium being deposited into tooth during the tooth's formation For further discussion, see text [from Albright (1937a)]

Phosphorus like calcium, is found in large amounts in bones and teeth (Ca P ratio approximately 2 to 1) and in small amounts in body serum. There, of prime concern to the subject under discussion, is the "inorganic" or "phosphate" phosphorus which hereafter will be called "serum phosphorus". The normal level for adults is 3.2 mg. plus or minus 0.5 mg. The level is 1 to 2 mg. higher in growing children. There are, in addition, in the body many organic phosphate compounds such as nucleo-protein, phospholipids, and various phosphate esters which liberate phosphate ions on hydrolysis. Thus, a negative phosphorus balance does not necessarily mean that phosphates are leaving the bones.

In Fig. 2 the body is simplified to a rectangular affair with four appendages. Whereas the fluid in the body is really divided into several compartments (serum, interstitial fluid, etc.), only one compartment—that of the serum—is represented separately in the diagram, as this compartment is easy to tap with a syringe in order to measure the substances in solution. The bone of the body is represented by a rectangular mass in the center of the body. Since adult bone is covered by two functionally very dissimilar surfaces, one where new bone is being laid down and one where old bone is being resorbed, these two surfaces are indicated. The gastro-intestinal tract, the kidneys and urinary passageways, and the teeth are also represented. The direction and speed of calcium exchange in the body is indicated by arrows and lines. It will be necessary now to examine each of these structures more closely.

(A) *Composition of Bone*

Bone consists of organic matrix and inorganic matter. The matrix is composed of a groundwork of osteocytes and intercellular substance, the inorganic matter consists chiefly of calcium, phosphate, and carbonate. Taylor and Sheard (1929) from a study of the refractive index and diffraction patterns of bone salts, concluded that the solid inorganic phase of bone, enamel, and dentine is composed of crystals of apatite minerals the general formula of which is $n\text{Ca}_3(\text{PO}_4)_2 \cdot \text{CaX}_2$. From chemical analysis and x-ray spectrograms Roseberry, Hastings, and Morse (1931) concluded that the calcium salts of bone and enamel may be represented by the formula $\text{CaCO}_3 \cdot n\text{Ca}_3(\text{PO}_4)_2$ (dahlite). In a later paper Bogert and Hastings (1931) concluded that n approximates 2 for untreated bone. The importance of all this as regards the subject matter to come is that bone inorganic matter is in the form of crystals, which at once suggests formation by precipitation and that the precipitation of the salt in question must be influenced by the calcium, phosphate, and carbonate ion concentrations of the fluid from which it is precipitated.

(B) *Bone Formation and Bone Resorption—Histological Aspects*

It is not proposed to discuss here how bone is formed from cartilage during the growth of the skeleton. The discussion is limited to how bone is added to or subtracted from in the adult skeleton. Under normal conditions bone is constantly undergoing metaplasia, i.e. it is being formed in some places and destroyed in others. It should be emphasized that bone is not either being formed or destroyed depending on the equilibria but that both processes are going on side by side at the same time. To be sure, at any one time one process may greatly exceed the other.

The actual bone tissue of the body has, of course, a huge surface area. In the cancellous bone the surfaces are greater per unit of bone than in compact bone. Bone surfaces can be divided into three types: those where bone is being laid down, those where bone is being resorbed, and those where the status quo is being maintained. Under normal conditions the last type of surface predominates.

On a surface where bone is being formed one sees with the microscope next to the completed bone a thin layer or seam of 'osteoid tissue' (see Fig. 2). The osteoid tissue represents extracellular, not yet-calcified organic substance which has been laid down by the osteoblasts. The latter are cells with single nuclei which lie in rows on the outside of the osteoid seams. The calcium salt, presumably dahlite, is deposited in the osteoid tissue and may be seen with the microscope in suitable preparations as fine specks on the inner edges of the osteoid seams (see Fig. 2).

On those surfaces where bone is being destroyed one sees foreign body giant cells or osteoclasts. There are at least three theories about these. The first, to which the authors rather incline, holds that the inorganic salt is removed from the matrix on these surfaces in accordance with the physical chemical laws which govern the equilibrium between the solid phase and the fluid (*vide infra*) and that the osteoclasts represent foreign body giant cells clearing up the debris of organic matrix, the second maintains that the osteoclasts by their own vital activity cause dissolution of bone, the third supposes that the osteoclasts represent conglomerations of the osteocytes after the inorganic material has disappeared. Such in brief is what one had learned about bone formation and resorption by microscopic methods. To this knowledge can be added some reasonably likely conjectures based on more circumstantial evidence.

(C) *Alkaline Phosphatase*

The question arises as to why dahlite can be deposited on osteoblastic surfaces at the same time as it is being absorbed from osteoclastic sur-

faces especially since both phenomena are probably occurring in the intimate relationship to the same body fluid. Presumably something takes place at osteoblastic surfaces favoring deposition. As will be discussed below, a local increase in calcium phosphate or bicarbonate ions would favor such precipitation. There is considerable evidence that actually there may be an increase in phosphate ions due to the enzyme alkaline phosphatase. This enzyme has the property of splitting inorganic phosphate off of organic phosphate compounds. It is found in sizeable amounts in the teeth, skeleton, intestinal tract, and the kidneys. There is normally a small amount in serum. In the skeleton and teeth it is only found when and where calcium is being deposited. The hypothesis, first suggested by Robinson (1923), holds that it is an enzyme made by the osteoblasts (or odontoblasts or adamantoblasts or cementoblasts) which by its action increases the inorganic phosphate locally in bone forming (or tooth forming) surfaces thus favoring dahlite deposition on said surfaces. The small amount of phosphatase in serum is probably a reflection of the phosphatase formation in bone. Thus the serum phosphatase level is high in those conditions where matrix is being laid down in excess (e.g. during growth rickets, osteomalacia, osteitis fibrosa generalisata, osteitis deformans, etc.). In the absence of any other cause for a higher phosphatase level such as liver disease or obstructive jaundice, *a high serum phosphatase level is probably indicative of increased osteoblastic activity.* The normal serum phosphatase level in adults is 3-5 Bodinsky units [Bodinsky (1933)] higher values (up to 10 Bodinsky units) are found in children.

There is one difficulty in the phosphatase theory just discussed namely that there is very little organic phosphorus in plasma (and hence presumably very little in interstitial fluid) for phosphatase to act upon. Gutman and Gutman (1941) have furnished the final piece of evidence for an hypothesis which may circumvent this difficulty. It is an established fact that cartilage preparatory to calcification accumulates stores of glycogen which disappear during the course of calcium deposition. This suggested that phosphoric esters formed during glycogen breakdown might serve as substrates for bone phosphatase. Thus the glycogenolytic cycle is initiated by the reaction $\text{glycogen} + \text{inorganic phosphate} = \text{glucose-1-phosphate}$ this reaction is catalyzed by the enzyme phosphorylase. Gutman and Gutman were able to demonstrate the presence of phosphorylase in growing cartilage and also in bone tissue but not in articular cartilage. Since enzymes catalyze a reaction in either direction it is possible and they point out evidence that supports the possibility, that phosphorylase and not phosphatase may be the important dephosphorylating enzyme. In summary therefore, the immediate cause of calcification may be a localized increase of phosphate ions this increase

may result from the splitting off of inorganic phosphate from organic phosphorus compounds by alkaline phosphatase and/or phosphorylase the substrates for these enzymes to act upon may be built up by the enzyme phosphorylase

(D) *Body Fluids and Substances Contained Therein*

We are really primarily interested with that part of the body fluid which is in contact with bone and with the substances in that body fluid which would favor or impede the precipitation or solution of dahlite. However, since that particular body fluid is not available for clinical study, one has to take the next best thing—the blood serum. Many of the inferences to be drawn depend on the assumption that any abnormality in the fluid in intimate contact with bone will be reflected in serum.

(1) *State of Calcium in Serum*

The calcium in serum is composed of three fractions: (1) calcium ions; (2) calcium bound to protein; and (3) an almost negligible diffusible but unionized fraction. The latter fraction is probably composed of a variety of substances such as calcium citrate, calcium salts of other organic acids, and possibly colloidal tertiary calcium phosphate. McLean and Hastings (1934) devised a method of measuring the calcium ion concentration in which the isolated heart of the frog was used as a biological indicator. Fortunately, however, it is not necessary to use this highly ingenious but quite difficult technique because knowing the total serum calcium and the serum protein, one is able to obtain quite accurately the $[Ca^{++}]$ from a chart (see Fig. 3) constructed by McLean and Hastings (1934).

(2) *Relation of Serum Calcium to Serum Phosphorus*

Since the inorganic matter of bones and teeth is composed of a crystalline salt which in solution would be decomposed into calcium phosphate and carbonate ions, since these same three ions are present in the serum, and since there is a constant interchange between the bones and the serum, one cannot escape the suggestion that for any one level of carbonate ions the levels of calcium and phosphate ions are dependent on some solubility product. The question is what solubility product? If one calculates the $[Ca^{++}]^*$ from the total serum calcium and serum protein values (*vide supra*) and if one assumes that all the inorganic phosphorus in the serum is actually present in the ionized form, then one can determine whether the ion products correspond to the solubility products for tertiary calcium

* The expression $[Ca^{++}]$ stands for calcium ion concentration.

phosphate ($\text{Ca}_3(\text{PO}_4)_2$) or for dahllite ($\text{CaCO}_3 \cdot 2\text{Ca}_3(\text{PO}_4)_2$) by the use of the following equations respectively.

$$(a) \quad [\text{Ca}^{++}]^2 \times [\text{PO}_4^{--}]^3 = K' \text{ s p } \text{Ca}_3(\text{PO}_4)_2$$

$$(b) \quad [\text{Ca}^{++}]^2 \times [\text{PO}_4^{--}]^3 \times [\text{CO}_3^{--}] = K' \text{ s p } \text{CaCO}_3 \cdot 2\text{Ca}_3(\text{PO}_4)_2$$

Unfortunately both these calculations leave the serum very much super-saturated which is unlikely. There are two lines of argument which

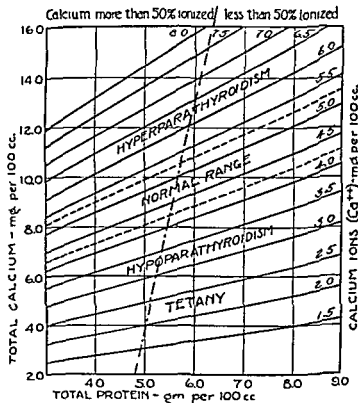


Fig 3 Chart for Determination of Calcium Ion Concentration from Total Protein and Total Calcium Values of Serum

[From McLean and Hastings (1935), with permission of the American Journal of Medical Sciences]

attempt to circumvent this difficulty which may be of interest to the more academically minded readers.

Albright, Bauer, Cockrill, and Ellsworth (1931) raised the question as to whether a fraction of the so-called inorganic phosphorus of the serum may not really be bound to protein, thus would explain the low spinal fluid inorganic phosphorus level. Another possibility is that there may be in

the serum an organic phosphorus compound which is quickly hydrolyzed after removal from the body (*cf* creatine phosphate). However, if one calculates the solubility products from the calcium and inorganic phosphorus values of spinal fluid, one still comes out with super-saturation.

Logan (1940) from a long series of experiments came to the conclusion that the precipitation of dahlite into bone consists of three steps. The first of these, as first suggested by Shear and Kramer (1928) is the precipitation of secondary calcium phosphate (CaHPO_4), the second step is the conversion of this into tertiary calcium phosphate ($\text{Ca}_3(\text{PO}_4)_2$) the final step is the adsorption onto a lattice work of tertiary calcium phosphate crystals of calcium carbonate or possibly of calcium hydroxide or even of primary calcium phosphate. It turns out that the serum is approximately saturated with respect to CaHPO_4 so it may be that its solubility product governs the levels of serum Ca and P.

In spite of the fact that the chemists and physicists have not come to any final conclusion as to just what equilibrium is involved, for the clinician the important inference is that the body fluids are either saturated or at a constant degree of supersaturation or undersaturation in respect to some salt of calcium and phosphate so that, in the absence of any fluctuation in the pH, a rise in the calcium ions will lead to a fall in the phosphate ions and *vice versa*. As a matter of fact for all practical purposes the adjustment of the total serum calcium to the serum phosphorus when both are expressed in mg per 100 cc is such that their product remains approximately constant (*circa* 30-40 for adults, 40-55 for growing children). This fact, of course, is the basis of the famous law of Howland and Kramer (1922) that rickets will be present in children if the above mentioned product is below 35 and will heal if it rises above 40.

(F) *Body Fluids and Electrolytes in Relation to Bone*

It is the authors' opinion that the kidneys under normal conditions keep the blood electrolytes at such levels that the interstitial fluid is constantly undersaturated with respect to dahlite so that normally there is a constant *dissolution of calcium and phosphorus from bone-resorbing surfaces*. It is clear that the rate of bone resorption will be increased by any influence which decreases in the body fluids the calcium ions, the phosphate ions, or the carbonate ions and *vice versa*. Thus an acidosis will hasten bone resorption (*cf* decalcification with ammonium chloride therapy). An influence which lowers the calcium ions but at the same time raises correspondingly the phosphate ions will not necessarily hasten bone resorption. It will depend on which factor is relatively the more changed (*cf* lack of decalcification with hypoparathyroidism).

Now when one comes to consider bone formation the situation is very

different. The rate of dahlite deposition is going to depend on the activity of the osteoblasts in laying down the organic matrix (osteoid). Once the matrix is laid down dahlite will be deposited in maximal amounts provided that the composition of the body fluids is not too abnormal. Pathologically (in rickets and osteomalacia) one encounters a situation where the body fluids are so low in pho-phate ions or pho-phate and calcium ions that, in spite of a presumably normal pho-phatase-pho-phorylase mechanism, precipitation of dahlite does not occur. This results in wide uncalcified osteoid seams (see Fig. 129, page 256). In other words any slight change in the ion product probably influences bone resorption; dahlite deposition, on the other hand, is influenced by the ion product only when a marked abnormality in the direction of unsaturation occurs.

The next question is: what influences osteoblastic activity? Certain nutritional and hormonal factors will be considered elsewhere. There is considerable evidence that mechanical stresses play a large part. If a bone is broken and set at a new angle the new bone is laid down in accordance with the new stresses involved. If an extremity is put into a cast, thus stopping all stresses, the bone loses calcium probably due to lack of bone formation rather than to increased bone resorption (see page 147).

In summary, then, bone consists of an organic matrix in which is deposited a calcium-phosphate-carbonate complex, called dahlite. Bone has bone-resorbing and bone-forming surfaces. The fluid in contact with bone is probably normally maintained by the kidneys at such a composition that dahlite is constantly being resorbed from bone-resorbing surfaces, the rate depending on minor fluctuations in the composition of the body fluids. Bone deposition occurs in response to stresses and strains wherever bone is needed. Of course, it will usually be needed approximately where it has been resorbed. Bone deposition consists in the laying down of the organic matrix rich in pho-phatase and possibly phos-phorylase by the osteoblasts; pho-phatase and possibly pho-phorylase by increasing the concentration of phosphate ions allow for the deposition of dahlite locally. This whole mechanism, it will be seen, constantly keeps the structure of the skeleton as efficient as possible for the need to which it is put, i.e. sufficiently strong but not needlessly bulky.

(F) Four Cardinal Metabolic Changes Induced by Parathyroid Hormone

If one removes the parathyroid glands from a normal human or, what amounts to the same thing, if one stops parathyroid extract therapy in a hypoparathyroid patient, four cardinal metabolic changes occur. There is first an immediate decrease in the phosphorus excretion in the urine; secondly the serum phosphorus level rises; almost simultaneously the serum

calcium level falls finally, with the fall of the serum calcium there is a diminished calcium excretion in the urine. If one administers parathyroid extract to a normal individual or to a hypoparathyroid patient the same four metabolic functions are altered in the opposite direction but in the same sequence that is one obtains consecutively changes in the direction of hyperphosphaturia hypophosphatemia hypercalcemia and hypercalcuria.

Fig 4 shows how these four variables—serum calcium serum phosphorus urinary calcium and urinary phosphorus—fluctuated in a hypoparathyroid patient before during and after parathyroid extract administration [Albright and Ellsworth (1929)]. The patient's day was divided into three eight hour periods. He received the same diet three times daily at the same relative time in each period. The urine for each eight hour period was analyzed for calcium and phosphorus. Note that the phosphorus excretion in the urine became maximal in the first eight hours after hormone administration that there was an abrupt fall in serum phosphorus with an almost simultaneous rise in serum calcium that the urinary calcium excretion did not rise until after the serum calcium had reached about 8.0 mg per 100 cc. In Fig 5 are recorded in graphic form the same variables on the same patient before and after the administration of a single dose of parathyroid extract. In this experiment however the urine collections were obtained every hour instead of every eight hours. Note that the hyperphosphaturia occurred in the first hour after injection of the hormone that the urinary calcium excretion did not increase during the duration of the experiment.

It is highly likely that these four cardinal metabolic changes following the administration of parathyroid extract (or the reciprocal changes following the cessation of treatment or the removal of the parathyroid glands) are interrelated phenomena. One cannot help believing that the serum phosphorus falls and rises as the serum calcium rises and falls in order to keep some solubility product constant.

If one takes the serum calcium and phosphorus values in Fig 4 and analyzes them more carefully it will be seen that the quotient of the serum calcium in mg per 100 cc multiplied by the serum phosphorus in mg per 100 cc in spite of the marked fluctuations in both values remained about 60 (see Fig 6A). If one takes these same figures and assumes that the calcium and phosphorus are entirely in an inorganic form and then calculates the $[Ca^{++}]$ the $[PO_4^{--}]$ and the $[HPO_4^{--}]$ one can construct curves (see Fig 6B and 6C) for the ion products in respect to $Ca_3(PO_4)_2$ and $CaHPO_4$ at different levels of serum $[Ca^{++}]$. The mean ion product for $Ca_3(PO_4)_2$ of these figures is 6.88×10^{-4} . This value agrees fairly well with that of 6.3×10^{-4} which was found by Brownian (1933) for similar calculations.

on the serum of normal individuals. However, from these calculations it appears that the serum would be tremendously supersaturated if the solubility product of $\text{Ca}_3(\text{PO}_4)_2$ ($= 3.02 \times 10^{-26}$ for serum) were governing the fluctuations of serum phosphorus with respect to calcium. From Fig 6B, furthermore, it is apparent that the curve is not the right shape, the serum phosphorus values do not rise sufficiently for low values of serum calcium.

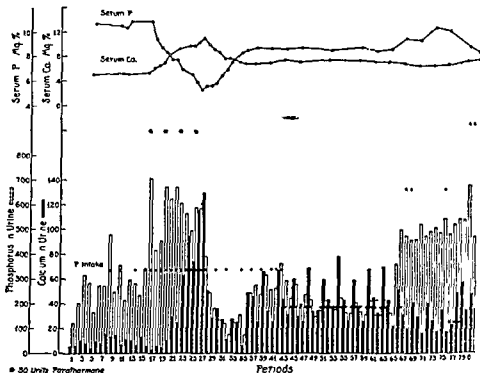


Fig 4 Effect of Parathyroid Extract on Urinary Calcium and Phosphorus Excretions and Serum Calcium and Phosphorus Levels in a Patient with Idiopathic Hypoparathyroidism

For further details see text. 50 units of parathyroid equal 250 units of parathyroid extract. [From Albright and Illsworth (1929)]

Similar calculations have been made for the ion products in respect to dahlite and similar objections were encountered to an even greater degree.

However, the mean value of the ion product in respect to CaHPO_4 was 2.01×10^{-6} . This compares reasonably closely with the solubility product (2.5×10^{-6}) of this salt for serum found by Logan (1940). Furthermore, (see Fig 6C) the shape of the curve fits the data much better.

It seems quite probable from these and other data that the fluctuations

in serum calcium and phosphorus in hypo and hyperparathyroidism are governed by some solubility product of some calcium and phosphorus salt. The next question is whether in parathyroid diseases the serum calcium adjusts to the serum phosphorus or whether the serum phosphorus adjusts to the serum calcium.

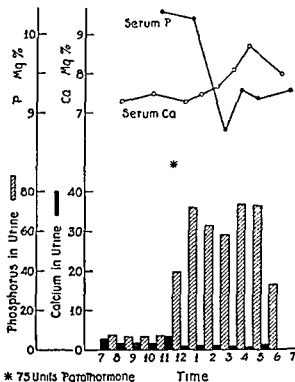


Fig. 5 Effect of Parathyroid Extract on Urinary Calcium and Phosphorus Excretions in a Patient with Idiopathic Hypoparathyroidism

See text for details. Data were obtained from same patient as those in Fig. 4 experiment differs from that experiment in that collections were made every hour instead of every eight hours. [From Albright and Lillsworth (1929)]

(G) The Mode of Action of the Parathyroid Hormone

There are two schools of thought in regard to the action of parathyroid hormone. One school believes that the hormone acts directly on bone tissue to cause its dissolution [Thomson and Collip (1932), and Jaffe (1933)], and that the electrolyte changes are secondary to the bone changes. Some members of this school believe that this dissolution is mediated by the osteoclasts. The other school, to which the authors are strong adherents, believes that the hormone acts on the electrolyte equilibrium of the body

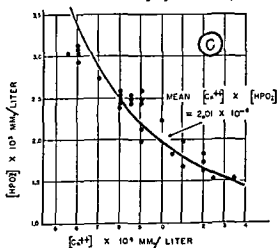
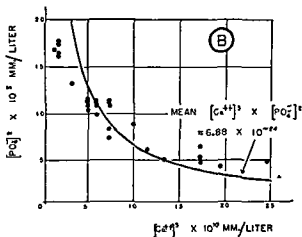
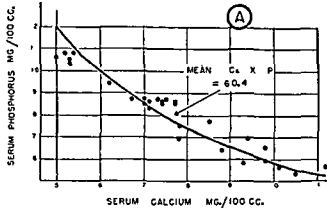


Fig 6 An Analysis of the Inter relation of the Calcium and the Phosphorus in the Serum at Various Levels of Parathyroid Insufficiency

In (A) the products of the calcium and phosphorus in mg are plotted against the mean product, in (B) the ion products with respect to $Ca_3(PO_4)_2$ are plotted against the mean product, and in (C) the ion products with respect to $CaHPO_4$ are plotted against the mean product. For further discussion, see text. The authors are indebted to Dr. Hirsch W. Sulkowitch for the preparation of this figure.

fluids and that the bone changes, when they occur, are secondary to the chemical changes. The argument will be confined to an elaboration of the second theory together with a few of the arguments pro and con.

The authors believe the sequence of events is something as follows: the parathyroid hormone in some way affects the phosphate dissolved in body fluids in such a way as to make it more readily excreted by the kidney, with a resulting decrease in the serum phosphorus level, this tends to make the body fluids less saturated in regard to whatever equilibrium constant governs the serum calcium and phosphorus values (*vide supra*), resorption of the calcium phosphate salt from the bone resorbing surfaces is thereby increased. There results an elevated serum calcium level together with the depressed serum phosphorus level. Once this new state of equilibrium has been reached there would be no further changes if it were not for the fact that the higher serum calcium level leads to an increased calcium excretion in the urine. This loss of calcium in the urine is a factor tending to cause undersaturation of the body fluids again so that unless there is a supply of calcium from the gastrointestinal tract the bones will have to supply the deficit, there will result, therefore, a decrease in the total amount of bone tissue and the bones will become weak. As the bones become weak they will be more subject to stresses and strains, this will stimulate the osteoblasts to lay down more osteoid tissue. The osteoid tissue laid down will be calcified since the local calcifying factor (phosphatase phosphorylase mechanism) will more than offset the decreased saturation. The drain of calcium and phosphorus into osteoid tissue will further tend to undersaturate the blood and hence further increase the bone resorption. The result, of course, is a vicious cycle as von Recklinghausen (1891) originally pointed out, from his studies on histological changes alone, there is a marked turn over of bone in this disease.

In considering the effect of metabolic disorders such as hyper- and hypoparathyroidism on bone tissue one must be careful to differentiate the effect on calcium resorption from that on calcium deposition. It is perfectly possible that a single disorder will at the same time increase calcium resorption and facilitate calcium deposition.

In the classical experiments of Shipley, Krumer, and Howland (1926), it was shown that a calcified rachitic cartilage placed *in vitro* in serum from normal animals took up bone salts but not when placed in serum from rachitic animals. McLean, Lipton, Bloom, and Barron (1916) showed that rachitic cartilage, when placed in serum from an animal made hyperparathyroid from hormone injections, took up bone salts more readily than when placed in serum from a normal animal. From this observation one might argue, as did McLean, that the parathyroid hormone leads to supersaturation of the blood with respect to calcium phosphate. This is at

variance with the thesis here propounded that the first action of the parathyroid hormone is to lead to increased phosphate excretion in the urine, which would be a step in the direction of undersaturation. Furthermore, the conclusion of Dr McLean is at variance with the clinical fact that hyperparathyroidism tends to cause bone resorption. We will attempt to present a scheme which brings these two points into harmony.

As discussed above we believe that the kidneys in their role of controllers of homeostasis keep the calcium and phosphate levels in the body fluids at such heights that calcium phosphate will be constantly resorbed at bone-resorbing surfaces. Thus constant bone resorption leads to a weakened skeleton which is more susceptible to stresses and strains. This, in turn, leads to the osteoblasts laying down matrix at the weakened spots. Where the osteoblasts lay down matrix there is a local calcifying factor which allows secondary calcium phosphate to be deposited there while dahlite is being resorbed on other bony surfaces.

Now for some simple arithmetic! Let us assume that the serum calcium in milligrams is proportional to the concentration of calcium ions and that the inorganic phosphorus in milligrams is proportional to the concentration of secondary phosphate ions. The quotients of the calcium in milligrams times the inorganic phosphorus in milligrams would then be an index to the degree of saturation of the body fluids with respect to secondary calcium phosphate. Let us make two further assumptions (1) that a calcium times phosphorus product of 60 is necessary for precipitation of secondary calcium phosphate and (2) that the local calcifying factor boosts the level of inorganic phosphorus locally 3 milligrams. These actual figures have no meaning but will serve to bring out the point. We then have the following equations:

Cal	um		Phosphorus		Product	Interpretation
A	10	×	4	=	40	(normal serum)
B	10	×	(4 + 3)	=	70	(normal serum plus boost from local calcifying factor)
C	20	×	2	=	40	(hyperparathyroid serum)
D	20	×	(2 + 3)	=	100	(hyperparathyroid serum plus boost from local calcifying factor)
E	2	×	20	=	40	(hypoparathyroid serum)
F	2	×	(20 + 3)	=	46	(hypoparathyroid serum plus boost from local calcifying factor)
G	8	×	1	=	8	(rachitic or osteomalacic serum)
H	8	×	(1 + 3)	=	32	(rachitic or osteomalacic serum plus boost from local calcifying factor)

It will be noted that, although normal serum, hyperparathyroid serum, and hypoparathyroid serum are equally saturated with respect to secondary calcium phosphate (equations A, C, and E), the local calcifying factor is much more effective with hyperparathyroid serum than with normal serum, and much less effective with hypoparathyroid serum than with normal serum (see equations B, D, and F). In the above arithmetic we have assumed that the low serum phosphorus of the hyperparathyroid state is completely compensated for by the high serum calcium, this is not true in all probability. For an inorganic phosphorus level of 2, one might take as a calcium figure 18. The products would then be 36 for the serum and 90 for the serum plus the boost from the local calcifying factor, the corresponding figures for normal serum are 40 and 70, respectively. Thus, the hyperparathyroid patient, as compared with the normal individual, would tend to pull calcium faster from bone resorbing surfaces and deposit it more rapidly in bone forming surfaces or in a calcified rachitic cartilage (cf. experiment of McLean). This agrees with the clinical fact that one can have in growing children generalized decalcification with hyperparathyroidism but normal deposition of calcium in the growing epiphyseal cartilage. It will be further noted that the local calcifying factor is relatively ineffective for the high serum phosphorus and low serum calcium levels of hypoparathyroidism. This probably explains the α -calcification obtained by Erdheim (1911) in the incisor teeth of rats deprived of their parathyroid glands (Fig 15, p 32). Finally it will be noted (see equation H) that in rickets or osteomalacia, in spite of a good boost from the local calcifying factor, the ion product to begin with is so small that precipitation of calcium is impossible.

So much for our conception of the mode of action of the parathyroid hormone, now for some of the arguments pro and con.

It will be noted, if our hypothesis is correct, that as a result of parathyroid extract the calcium rises because the phosphorus falls, not *vice versa*. Regardless of any experimental evidence (*vide infra*) this is the more logical of the two possibilities. The tendency with parathyroid extract is to pull calcium from the bone. If the first effect of the hormone were an increase in serum calcium this would be a change in the direction of supersaturation which would immediately tend to stop bone resorption and the whole process would stop. However, if the first step is to lower the serum phosphorus level, a change in the direction of undersaturation results, which would increase the pull of calcium and phosphorus into the body fluids either from the bone or from the gastrointestinal tract. Similarly, it will be noted that as a result of removing the parathyroid glands from an individual the calcium falls because the phosphorus rises, not *vice versa*. This means that the tendency is to supersaturation. This, in turn, could

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E 2 × 20 = 40		(hypoparathyroid serum)	
F 2 × (20 + 3) = 46		(hypoparathyroid serum plus boost from local calcifying factor)	
G 8 × 1 = 8		(rachitic or osteomalacic serum)	
H 8 × (1 + 3) = 32		(rachitic or osteomalacic serum plus boost from local calcifying factor)	

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explain the tendency in hypoparathyroidism for bone to be dense and for calcium to be deposited in abnormal locations (*vide infra*)

The fact that the first sequela of parathyroid extract administration is an increase of the phosphorus excretion in the urine (see Fig 4 and 5) is strong evidence in favor of the above hypothesis. Furthermore, when one administers parathyroid extract to normal individuals one also obtains an initial washing out of phosphorus from the body fluids (see Fig 7). Note in Fig 7 the marked rise in serum calcium and in the urinary calcium excretion and the lack of any marked effect on the fecal calcium excretion following administration of the hormone; secondly, note the marked rise in urinary phosphorus excretion and the fall in the serum phosphorus level. But the important question to determine from the data presented in Fig 7 is whether the effect on calcium metabolism is greater and more prompt than on phosphorus metabolism or whether the converse is true. With the actual phosphorus balance (i.e. intake minus output in urine and feces), period by period is plotted the "theoretical phosphorus balance." Since this latter term is discussed extensively in the appendix, page 303 it will be mentioned here only briefly. The phosphorus in the body can be divided into three parts: that deposited with calcium in the bones (Ca/P ratio = 2.23), that built into protoplasm (N/P ratio = 14.7), and all the remaining phosphorus which is mostly in the form of phosphates dissolved in the body fluids. By "theoretical phosphorus balance" is meant that part of the phosphorus balance that can be explained by the calcium balance and the nitrogen balance. Therefore, if the actual phosphorus balance were greater than the theoretical phosphorus balance the inference would be that phosphate in body fluids was being increased. It has been clearly demonstrated in Fig 7 and by other data [Albright, Bauer, Ropes, and Aub (1929)] that during the first few days after onset of parathyroid extract administration to normal individuals the actual phosphorus balance is less than the theoretical balance and that the opposite is true for the first few days after cessation of parathyroid extract administration. Those who believe parathyroid extract acts directly on bone tissue might argue that calcium is dissolved from bone by the hormone but that the phosphate is excreted more readily than the calcium. Against this argument is the fact that when calcium is dissolved as the result of acidosis, as with ammonium chloride administration, the calcium and phosphorus excretions are simultaneous [Albright, Bauer, Ropes, and Aub (1929)].

Whereas the theory which holds that the parathyroid hormone acts directly on bone tissue might possibly explain the high serum calcium with hyperparathyroidism and the low serum calcium with hypoparathyroidism how is it to explain the low serum phosphorus with hyperparathyroidism and the high serum phosphorus with hypoparathyroidism?

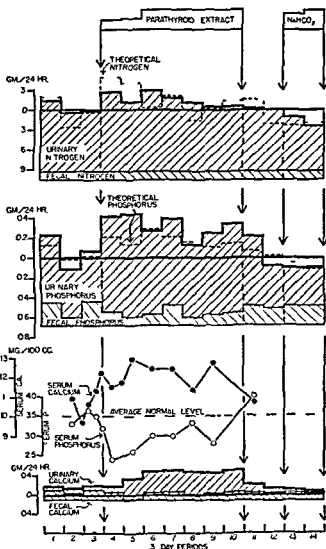


Fig 7 Data Showing Effect on Calcium and Phosphorus Metabolism of Parathyroid Hormone Administered to a Normal Individual

Note that the theoretical phosphorus balance is less than the measured phosphorus balance when parathyroid hormone (250 to 500 units per day) is first administered, and that the theoretical phosphorus balance rises above the measured phosphorus balance after cessation of the hormone administration. For methods of charting this and all subsequent metabolic data in this book, see Appendix, page 300. [Recharted from Albright, Bauer, Ropes, and Aub (1929), see also Reifenstein, Albright, and Wells (1945)]

There is a group of observations which emphasizes the importance of the changes in the phosphorus metabolism. Harrison and Harrison (1911),

working on dogs were able to show that parathyroid hormone causes a decreased reabsorption of phosphorus in the kidney tubules. Tepperman, L'Heureux, and Wilhelm (1947) developed a test for parathyroid hormone which depends upon lowering of the serum phosphorus level in rats. Brown and Imrie (1932) showed that parathyroid hormone increased the affinity of creatine for phosphoric acid in decerebrate cats.

To the above arguments can be added a few derived from the clinic. If the first sequelæ to the administration of parathyroid hormone is a phosphate diuresis, one should be able to force feed phosphate to such a degree that this property is offset. This in turn should prevent the lowering of the serum phosphorus level and interfere with the other sequelæ. With this in mind Albright, Bauer, Claflin, and Cockrill (1932) were able to raise the serum phosphorus level with a high phosphate intake in patients with hyperparathyroidism and in so doing to reduce both the high serum calcium level and the high urinary calcium excretion to normal (see Fig. 8).

In patients with renal insufficiency and resulting phosphate retention it is impossible to raise the serum calcium with parathyroid extract (unpublished data). This is consistent with the hypothesis that the initial action of the hormone is to increase the excretion of phosphates and once this has been interfered with no other sequelæ can occur.

Many patients with severe and long standing hyperparathyroidism never do develop any bone disease (see page 67). This suggests that the bone disease when present is a secondary complication, not the primary disorder.

Finally, the fact that the number of osteoclasts seen in experimental hyperparathyroidism depends on the duration of the hyperparathyroidism is evidence against the conjecture that the osteoclasts by their own vital activity are the cause of bone destruction in this condition. If such were the case one should find just as many osteoclasts early in the condition when the serum calcium and the urinary calcium excretion are maximal as late in the disease.

There are a few observations on the other hand which are more easily explained on the assumption that the hormone does act directly on bones.

Ellsworth and Fletcher (1935), in nephrectomized dogs were able to demonstrate a rise in serum calcium following parathyroid hormone administration. Moreover, Collip, Pug-Jev, Selye, and Thomson (1931) and McLunkin, Tweedy, and McNamara (1937) were able to produce bone changes in nephrectomized animals with parathyroid hormone. However Collip *et al.* did not publish results with nephrectomized controls and the possibility existed that nephrectomy alone with its concomitant acidosis might lead to bone resorption, McLunkin *et al.* did publish results on nephrectomized controls but their control animals were considerably heavier and presumably more mature than the experimental animals.

Therefore, one of the authors and his associates [Ingalls, Donaldson, and Albright (1943)] repeated and extended these observations and demonstrated that parathyroid hormone does have a direct decalcifying effect on

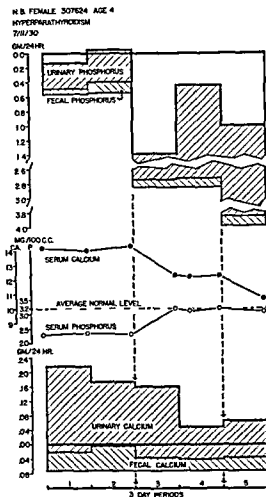


Fig. 8 Effect of Phosphate Ingestion on Disordered Homeostasis in Hyperparathyroidism

With the onset of high phosphate intake in period 3 note (a) strongly positive phosphorus balance (b) rise of serum phosphorus level to normal (c) fall in serum calcium level, and (d) fall in urinary calcium excretion [Redrawn from Albright, Bauer, Claffin, and Cockrill (1932)] (Patient N. B. M. G. H. 307624)

bones, even in the absence of the kidneys, and that this effect is independent of the acidosis produced by nephrectomy and of the acidosis produced by the acidity of the parathyroid hormone extract

Secondly, patients with hyperparathyroidism and bone disease shortly following the removal of parathyroid tumor, regularly show a fall in both the serum calcium and serum phosphorus levels while the bone tissue by biopsy shows a complete disappearance of all osteoclasts (see Fig 51, page

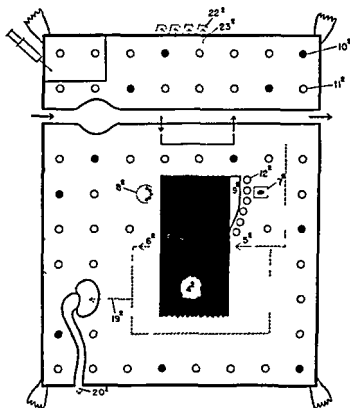


Fig 9 Diagrammatic Representation of Calcium Metabolism in Hypoparathyroidism to be Contrasted to That in a Normal Individual (Fig 2) and That in Hyperparathyroidism (Figs 10 and 11)

Note decrease in the number of calcium ions in body fluids (10) increase in number of phosphate ions in body fluids (11) absence of calcium excretion in the urine (20) decrease in bone resorption (6-) with a decrease in osteoclastic activity (8-) resulting increase in bone mass (4) and compensatory decrease in bone formation with decreased osteoblastic activity (7) Note also decreased deposition of calcium into teeth (23) with resulting a calcification of teeth (22) [From Albright (1947a)]

110) This failure of the serum phosphorus to rise is hard to explain but the authors are inclined to believe that for some reason or other the serum phosphorus level under these circumstances is not a true reflection of the interstitial fluid phosphorus level. In these cases as shown below (Fig 50 page 108) the decrease in the phosphorus excretion in the urine is out of

proportion to the decrease in calcium excretion in spite of the failure of the serum phosphorus to rise it is thus clear that phosphorus is being retained somewhere. Furthermore, in patients with hyperparathyroidism but no bone disease the serum phosphorus level does rise promptly on removal of the parathyroid tumor.

Thirdly, the fact that one has osteitis fibrosa in renal osteitis fibrosa (see page 115) together with hyperplasia of the parathyroid glands at least suggests that the bone lesions are due to the parathyroid hormone, there are other possibilities.

Fourthly, in unpublished experiments in which the hyperphosphatemia of hypoparathyroidism was eliminated by ingestion of aluminum hydroxide which prevents the absorption of phosphates, the rise in serum calcium was not as marked as the authors would have liked.

One of the authors (F. A.) has attempted to reconcile the two schools of thought with the suggestion that parathyroid hormone may act primarily on phosphorus metabolism in some way which not only increases the excretion of phosphorus in the urine but also produces certain bone changes directly. It is amusing that just as the authors have had to admit that there may be a direct action on bone tissue (*vide supra*) the chief proponent of the other school Dr J. B. Collip [Neufeld and Collip (1942)] has swung around somewhat to the authors' original point of view. The authors still feel that the main action of the parathyroid hormone is on the phosphorus and calcium metabolism.

II. PATHOLOGIC PHYSIOLOGY

Figs. 2, 9, and 10 serve as sort of animated cartoons of what is taking place in adult bone in isoparathyroidism, hypoparathyroidism and hyperparathyroidism with bone disease respectively. It should be noted that hypoparathyroidism is associated with a tendency to supersaturation of the blood (i.e. serum phosphorus level rises first and serum calcium level falls secondarily). One would expect, therefore, a decreased bone resorption; this in turn would make the bones less subject to stresses and strains so that bone deposition would also be decreased. Thus in hypoparathyroidism one would expect only a slight increase in the density of the bone, this is true.

Since, according to our thesis, parathyroid hormone does not act directly on bone tissue but rather creates a disturbance in homeostasis which leads to an increased loss of calcium and phosphorus in the urine, one would anticipate that cases of hyperparathyroidism would occur in which the individuals because of a high calcium and phosphorus intake would have no bone disease. Such is the case. In Fig. 11 this situation is diagrammatically shown.

III CHEMISTRY AND ASSAY OF PARATHYROID HORMONE

The active principle of the parathyroid gland was first extracted by Hanson (1923) and later by Collip (1925). The latter used acid extraction and

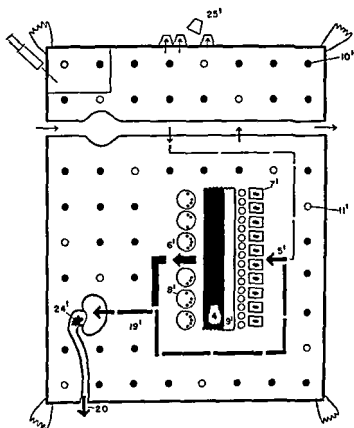


Fig 10 Diagrammatic Representation of Calcium Metabolism in Hyperparathyroidism With Bone Disease to be Compared with Calcium Metabolism in the Isoparathyroid State (Fig 2)

Note decrease in bone mass (4), increase in number of calcium ions in body fluids (10), decrease in number of phosphate ions in body fluids (11), increased calcium resorption from bone resorbing surfaces (6), increased number of osteoclasts (8), increase in bone formation with large number of osteoclasts (7), ability of calcium to be deposited in the newly formed osteoid tissue as shown by arrow 5, an normal width to osteoid seams (9), tendency to kidney stone formation (24), and absence of decalcification in teeth although an individual tooth may fall out because of faulty bone (25). [From Albright (1947a)]

isoelectric precipitation. The dried product prepared by Collip's method contains about 15.5 per cent nitrogen and traces of iron and sulphur. It is an amorphous powder, each unit weighing 0.3 mg. It is soluble in water and

in 80% alcohol but insoluble in ether, acetone, and pyridine. It gives most of the common color reactions for protein, its potency is destroyed by heating for an hour with 10 per cent hydrochloric acid or 5 per cent sodium

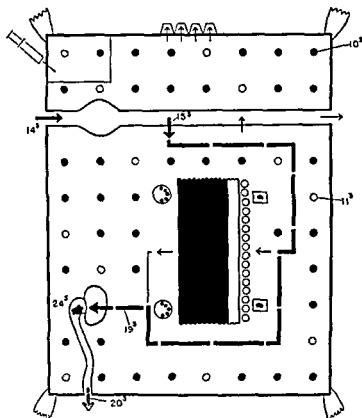


Fig 11 Diagrammatic Representation of Calcium Metabolism in Hyperparathyroidism Without Bone Disease to be Compared with Calcium Metabolism in Normal State (Fig 2) and That in Hyperparathyroidism With Bone Disease (Fig 10)

Note that condition coincides with hyperparathyroidism with bone disease in having an increased number of calcium ions in body fluids (10³), a decrease in phosphate ions (11³), an increase of calcium excretion in the urine (20³) and a kidney stone (21³), note, however, that there is no diminution in bone mass, no increase in bone destruction or in bone formation and that increased calcium excretion in the urine is entirely supplied by increased calcium intake and absorption (14³ and 15³) [From Albright (1937a)]

hydroxide, and by incubation with pepsin or trypsin [Thomson and Collip (1932)]

There are three potent preparations on the market: Parathyroid Extract—Lilly, Parathyroid Hormone—Squibb, and Paroidin—Parke Davis, and

Company All are for subcutaneous or intramuscular use The Lilly unit is defined as 1/100th the amount of extract required to cause an increase of 1 mg of calcium per 100 cc of blood serum of a dog weighing 20 kilograms the increase being determined after subcutaneous administration to dogs of sufficient quantities of solution to cause an average increase in blood serum calcium of from 4 to 6 mg within sixteen hours The Squibb and Parke Davis and Co units are very similar It should be noted that the term, "Parathormone—Lilly", is no longer used One hundred units of Parathyroid Extract—Lilly are the equivalent, however, of 20 units of the old "Parathormone"

Parathyroid Solution (Extract) U S P, is the official preparation available It is standardized by biologic assay so that 1 cc exerts the specific activity of 80 to 120 units Each unit is 1/100th of the amount required to raise the calcium level of 100 cc of the blood serum of normal healthy male dogs weighing 10 to 12 kg 1 mg within 16 to 18 hours after subcutaneous injection Parathyroid extract is active after an initial injection, but becomes less effective following repeated injections (> 'antihormone' formation) The extract is inactive by mouth

CHAPTER 2

CLINICAL HYPOPARATHYROIDISM

I HYPOPARATHYROIDISM

(A) *Etiology*

The accidental removal of or damage to the parathyroid glands in the course of a thyroid operation is of course the commonest cause for hypoparathyroidism. Not infrequently the malady when thus produced is transient the damaged glands apparently regenerating after several months. Very rarely hypoparathyroidism occurs idiopathically [Drake Albright, Bauer and Castleman (1939)]. Just why all four glands should cease to function is of considerable academic interest. In an autopsy on one such case all four glands were found to be present and grossly to have a normal appearance. However histological sections showed that the epithelial cells had been entirely replaced by the fat cells. An intermediary stage in which the epithelial cells were much diminished and replaced by fat has been described in a patient suffering from anterior pituitary insufficiency [Castleman and Hertz (1939)]. In panhypopituitarism however one does not find evidence of hypoparathyroidism and the authors do not believe that idiopathic hypoparathyroidism is due to lack of some tropic hormone from the anterior pituitary.

Sutphin, Albright, and McCune (1943) reported five cases of idiopathic hypoparathyroidism associated with moniliasis. Three of the five cases occurred in siblings. Talbot, Butler and MacLachlan (1943) had previously published two cases of moniliasis associated with Addison's disease in one of whom hypoparathyroidism was co-existent. Whether this extraordinary association of hypoparathyroidism with moniliasis was coincidental or was due to a predisposition of a patient with moniliasis to hypoparathyroidism or *vice versa* Sutphin *et al* were unable to decide. However the time relationships in the case histories suggested that the moniliasis preceded the hypoparathyroidism.

There is considerable evidence that the parathyroid glands may be functionally deficient in infants shortly after birth and that convulsions in such infants may be a manifestation of a hypoparathyroidism [Bakwin (1939)]. Of considerable academic interest is a case recently reported in which hypoparathyroidism developed in a child born of a hyperparathyroid mother [Friderichsen (1939)]. The inference of course was that the infant's parathyroids became compensatorily atrophied in intrauterine life.

There seems to be a definite tendency for idiopathic hypoparathyroidism to be associated with Addison's Disease. This subject was recently re-

viewed by Leonard (1946) who presented the clinical history and autopsy findings on one case. There was no doubt about the hypoparathyroidism from the clinical findings and no parathyroid tissue was found at autopsy, the adrenal cortices at autopsy showed complete destruction with replacement by connective tissue and with round cell infiltration. This adrenal pathology is often incorrectly spoken of as "adrenal atrophy."

(B) *Symptomatology*

The most striking clinical feature of hypoparathyroidism is the increase in neuromuscular excitability dependent on the hypocalcemia and producing the symptom complex known as tetany. The first and most constant feature of this complex is numbness of the extremities. Other symptoms more or less in order of appearance as the degree of hypoparathyroidism becomes more severe are cramps of the extremities, carpal pedal spasm, laryngeal stridor, and generalized convulsions. Tetany is seldom fatal but, when it is, the cause is usually asphyxia due to laryngeal spasm. One patient with laryngeal stridor was admitted to the Massachusetts General Hospital under the faulty diagnosis of bronchial asthma for which she had been treated for some time. "Epilepsy" may be the only symptom. The authors have seen one case which had had "epilepsy" for several years before the diagnosis was made. If untreated for a long period of time, mental retardation usually ensues.

Cataracts are a very common complication of hypoparathyroidism. They are apparently due to the hypocalcemia and tetany rather than to the hypoparathyroidism *per se* because they are met in other conditions with hypocalcemia and tetany, notably sprue.

Symmetrical, bilateral, punctate calcifications of the basal ganglia of the brain tissue which give a characteristic picture by x ray (see Fig. 12), are not uncommon [Eaton and Haines (1939), Siglin, Eaton, Camp, and Haines (1947)]. The authors consider this as one more piece of evidence that the changes in hypoparathyroidism are in the direction of supersaturation of body fluids with calcium phosphate (*vide supra*).

Increased intracranial pressure with bilateral choked discs is another bizarre finding and, when associated with epilepsy, often leads to the mistaken diagnosis of brain tumor [Barr, MacBrade, and Sanders (1935)].

Multiple ectodermal lesions are not infrequently met as in the cases reported by Emerson, Walsh, and Howard (1941), and Learner and Brown (1943). The patient presented by Emerson *et al.* had a dry, coarse and scaly skin, the hair was thin and patchy on the head and absent in the axilla and pubic regions, the eyelashes and eyebrows were scanty. The finger and toe nails were likewise atrophied and somewhat suggestive of the appearance presented by phytosis or moniliasis of the nails.

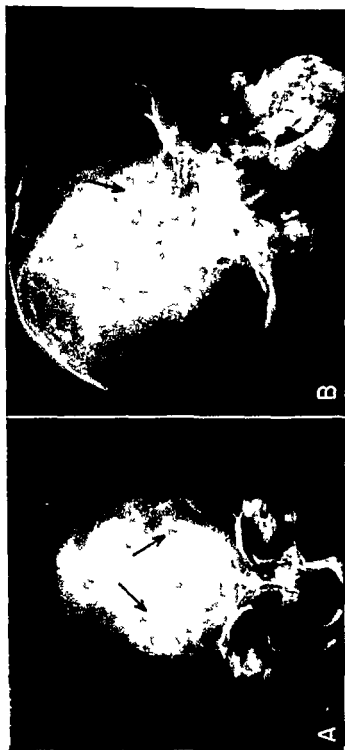


Fig 12 Calcification of Basal Ganglia of Brain in Hypoparathyroidism (Patient W C MGH 14727)

view these dental changes are most interesting since the first observation to connect the parathyroid glands with calcium metabolism was that of Erdheim (1911) in Vienna when he demonstrated a calcification of the den-



Fig. 14 X-ray Film (B) of Teeth of Patient M. G. H. 8568 with Idiopathic Hypoparathyroidism Compared with Film (A) of Teeth of Normal Subject

Patient was first seen at the age of 18 years with a history of 4 years duration. Note blunted ends of teeth in (B) compare with Fig. 13

tine of rats teeth following parathyroidectomy. These observations of Erdheim were extended in 1929 by Erdheim and Albright (unpublished data) when they showed that the calcification ceased when the parathyroidectomized rat received parathyroid hormone (see Fig. 15)

When hypoparathyroidism develops before the teeth have entirely formed one finds aplasia or hypoplasia of the teeth starting at that point in their development where the hypoparathyroidism came in [Albright and Strock (1933)] Thus, if a child develops the disease at about ten the teeth will be entirely normal except for a blunting of the roots of the molar teeth,

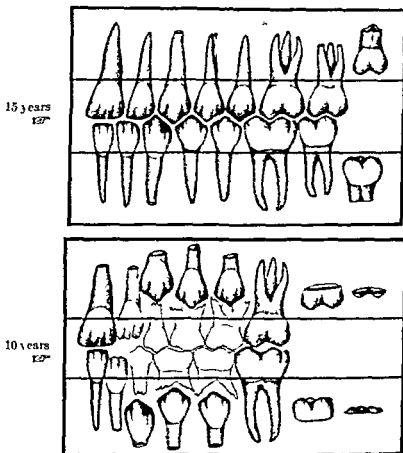


Fig 13 Chart Showing Development of Teeth at 10 Years (Below) and at 15 Years (Above)

Note the under developed roots of all except the first molar permanent (shaded) teeth at 10 years compare with Fig 14 [From Brady (1921)]

the last parts of the teeth to form (see Fig 13 and 14) This a-calcification of the teeth in hypoparathyroidism may seem a little surprising when one remembers the tendency to decalcification of the bones in hyperparathyroidism The authors' explanation is discussed on page 17 under 'Mode of Action of the Parathyroid Hormone' From an historical point of

view these dental changes are most interesting since the first observation to connect the parathyroid glands with calcium metabolism was that of Erdheim (1911) in Vienna when he demonstrated a calcification of the den-



Fig 14 X ray Film (B) of Teeth of Patient M G H 8568 with Idiopathic Hypo parathyroidism Compared with Film (A) of Teeth of Normal Subject

Patient was first seen at the age of 18 yr with a history of 4 years duration. Note blunted ends of teeth in (B), compare with Fig 13

tine of rats teeth following parathyroidectomy. These observations of Erdheim were extended in 1929 by Erdheim and Albright (unpublished data) when they showed that the a calcification ceased when the parathyroidectomized rat received parathyroid hormone (see Fig 15)

One would expect the bones to show slightly increased density in hypoparathyroidism (*vide supra*), and they actually do in most instances, although in any one case this might be a hard point to be sure of [Emerson Walsh, and Howard (1941)] In rare instances one finds osteomalacia associated with hypoparathyroidism, the explanation for this occurrence is probably the same as for the α -calcification of the teeth in parathyroidectomized rats (*vide supra*)

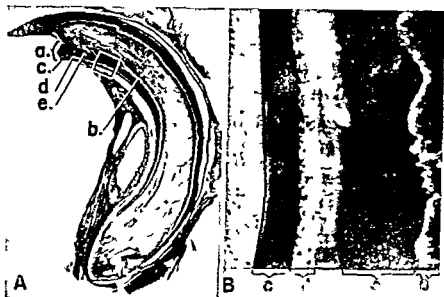


Fig 1a Effect of Parathyroidectomy and of Parathyroid Extract on Calcification of the Dentine of a Rat's Tooth

The rat was parathyroidectomized and after a period of two weeks was treated for two weeks with daily injections except for Sundays of parathyroid extract

- A Sagittal section through tooth a—dentine b—uncalcified dentine or dentinoid c—band of calcified dentine laid down before parathyroidectomy d—band of uncalcified dentine laid down during the period of parathyroid hormone insufficiency, e—band of calcified dentine laid down during period of parathyroid hormone injections
- B Higher power of boxed off area in A Note two faint lines (see arrows) of uncalcified dentine in the zone representing two Sundays when the rats did not receive injections (Frdheim, J., and Albright F. Unpublished Data)

(C) Physical Signs to Elicit Tetany

There are three classical signs which are used to elicit latent tetany and which are, therefore, to be looked for when hypoparathyroidism is suspected

Chrostek's sign [Chrostek (1876)] is elicited by tapping over the facial

nerv. in front of the ear, a positive result consisting of a twitching of the facial muscles, notably those of the upper lip. The test is almost invariably positive in untreated hypoparathyroidism of a marked degree. The authors, however, have seen one case in which it was not positive. Some normal adults give positive tests although this is said not to be true in normal infants. Three degrees of Chvostek's sign are sometimes recognized. Chvostek I—contraction of the muscles of the eyelids, of the alae nasi, and of the corner of the mouth, Chvostek II—contraction of the muscles of the alae nasi and of the corner of the mouth and Chvostek III—contraction of the muscles of the corner of the mouth only. Chvostek II and III are seen not uncommonly in normal individuals, Chvostek I is rarely present except in untreated hypoparathyroidism.

Trousseau's sign [Trousseau (1860)] is elicited by reducing the circulation in the arm by means of a blood pressure cuff whereupon if the test is positive, the hand assumes the position seen with carpopedal spasm,—namely a flexion at the wrist with fingers flexed at the metacarpo phalangeal joints but extended at the interphalangeal joints. The authors usually keep the pressure in the cuff above the systolic blood pressure and allow three minutes before calling the test negative. This test is frequently not positive in well marked cases of hypoparathyroidism.

Erb's sign [Erb (1876)] consists of an increased excitability of the motor nerves to galvanic current. The test is considered positive if the cathodal opening contraction, which normally requires more than 6 milliamperes, is obtained with less stimulation than 5 milliamperes. Anodal hyperexcitability is present also. This test is academically interesting but superfluous.

The Q-T interval in the electrocardiogram is prolonged because of the hypocalcemia [Kellogg and Herr (1936), Graybiel and White (1941)].

(D) Diagnosis

Once the condition is suspected from the clinical symptomatology the diagnosis is confirmed if it need confirming by the characteristic chemical findings,—namely a low serum calcium, a high serum phosphorus, a normal or even low serum phosphatase level and usually an absence of calcium in the urine. One can, of course, have any degree of hypoparathyroidism its severity roughly paralleling the degree of depression of the serum calcium value. In a totally a parathyroid patient the serum calcium will fall as low as 4.5 mg. per 100 cc. and the serum phosphorus level may reach 12 mg. per 100 cc. The serum phosphorus in older patients does not reach as high a level as it does in children (6 mg. \pm as opposed to 12 mg. \pm). Because of the decrease in osteoblasts (see Fig. 9, p. 22), one would expect the serum phosphatase level to be low and, as a matter of fact, it does seem to be slightly low in many patients.

If the serum calcium is below 7 to 8 mg per 100 cc, the threshold for calcium excretion, there will usually be an absence of calcium in the urine which can be easily determined by the use of the Sulkowitch reagent (see page 302). This is a solution containing oxalate radical buffered at such a pH that when equal amounts of the reagent are added to the urine the calcium will almost immediately come down as a fine, white precipitate of calcium oxalate. One can differentiate with this reagent (A) urine with virtually no calcium, (B) urine with small amounts of calcium and (C) urine with large amounts of calcium. A urine with no calcium in it is almost pathognomonic of hypocalcemia and, hence, if one can rule out other causes for hypocalcemia, is strong evidence in favor of hypoparathyroidism. A urine with only moderate amounts of calcium in it is strong evidence against hypocalcemia of any but a very slight degree; incidentally, it practically rules out hyperparathyroidism. A urine with large amounts of calcium is strong evidence against hypoparathyroidism consistent with the normal state, and quite suggestive of hyperparathyroidism or some other metabolic disease associated with hypercalcaemia (*vide infra*). Needless to say, if the patient has drunk a lot of milk on the day of the test the urine will contain more calcium unless the patient has hypocalcemia when it should make no difference.

The authors have encountered three cases of hypoparathyroidism who excreted large amounts of calcium in the urine at low levels of serum calcium. This phenomenon was apparently associated with an acute *coccal* pyelonephritis in one case and disappeared when this was alleviated by Penicillin therapy. No explanation was found in the other two cases. For a further discussion see "Idiopathic Hypercalcaemia", page 260.

(E) *Differential Diagnosis*

Other conditions which cause tetany may be confused with hypoparathyroidism. For all practical purposes one can consider that there are two causes of tetany: hypocalcemia and alkalosis. As far as the authors are aware there is no convincing evidence that the tetany due to alkalosis is entirely due to some secondary change in the availability of calcium ions.

The causes for hypocalcemia other than hypoparathyroidism are rickets (or its adult form osteomalacia) with its various etiologies including steatorrhea (see section on "Osteomalacia" page 217) and renal insufficiency with urea and phosphate retention. In rickets or osteomalacia the low serum calcium value is characteristically coupled with a low or, in some instances a normal serum phosphorus value. High serum phosphorus values are most unusual. The serum phosphatase level, which is normal or even low in hypoparathyroidism, is high in both rickets and osteomalacia. Steatorrhea, of which sprue is an example, probably leads to hypocalcemia because

vitamin D being fat soluble is dissolved in the unabsorbed fat. The condition, hence, results in hypovitaminosis D, the blood chemical findings therefore, are those of *osteomalacia*. In addition one may find evidence of the lack of other fat soluble vitamins, notably vitamin K (hemorrhagic diathesis) and vitamin A (night blindness, keratosis pilaris, etc.) [Albright and Stewart (1940)]

In renal insufficiency with azotemia one finds phosphorus retention with a compensatory lowering of the serum calcium level. There is however, in renal insufficiency as compared with hypoparathyroidism a lesser degree of hypocalcemia for the same degree of hyperphosphatemia. One seldom meets tetany in renal insufficiency with hypocalcemia because of the associated acidosis which inhibits tetany.

The commonest cause of tetany due to alkalosis is hyperventilation, usually the result of some emotional disturbance. The diagnosis is very simple. The respirations may be very rapid, in some cases however, they are merely a little deep and not so strikingly rapid. There may be a past history of similar attacks under emotional stress. The condition responds quickly to holding the breath or rebreathing into a paper bag. The urine, characteristically, is alkaline and contains normal amounts of calcium. The presence of calcium in the urine can be quickly verified by the aid of Sulkowitch solution (*vide supra*). In hyperventilation the CO_2 combining power of the serum may be only slightly reduced. The most significant change in the serum is a lowering of the CO_2 content of the arterial blood [Talbot, Cobb, Coombs, Cohen and Consolazio (1938)]. A less common form of alkalosis tetany is that due to ingestion of large amounts of alkali, where one encounters an alkaline urine, calcium in the urine, high CO_2 combining power of the serum and possibly a high serum total base value. In alkalosis due to excessive loss of gastric contents one again encounters an alkaline urine, calcium in the urine and an increase CO_2 combining power of the serum, this time combined with a lowering of the serum chloride value and possibly, of the serum total base value as well.

The differentiation between hypoparathyroidism and pseudo hypoparathyroidism will be discussed below under 'Pseudo-hypoparathyroidism', page 40

(F) Treatment

The treatment of hypoparathyroidism has been entirely revolutionized since the advent of dihydrotachysterol [Albright (1939)]. A short digression on this subject, therefore, seems in order.*

* The action of dihydrotachysterol is discussed more fully in the chapter entitled "Mode of Action of Vitamin D and Dihydrotachysterol (A T 10)", page 122

Dihydrotachysterol or A T 10 ('antitetanisches Präparat Nr. 10'), like vitamin D, is a photochemical derivative of ergosterol. Its development was based on the suggestion that the toxic and anti rachitic effects of vitamin D are due to two different properties. The previous conception had been that the toxic manifestations—calcium deposits in various organs and hypercalcemia—were due to an overabundance of the anti rachitic factor—hence, to a hypervitaminosis (see page 95). The toxic factor was designated by the German workers as 'Calcinosefaktor'. A T 10 was developed by Holtz (1933). It was thought to contain a large amount of the 'Calcinosefaktor' which, it was hoped, would be beneficial in the treatment of hypoparathyroidism, such proved to be the case.

Extensive studies were carried on at the Massachusetts General Hospital to determine just how the action of A T 10 differs from that of vitamin D and some rather definite conclusions were arrived at. First it was determined that vitamin D has two primary actions which are not related to each other but upon which all other sequelae following its administration depend [Albright and Sulkowitch (1938)]. These actions are to increase calcium absorption from the gastro-intestinal tract and to augment phosphate excretion into the urine. The former alone is anti rachitic, the latter explains the demineralization one gets from excessive doses of vitamin D. Now A T 10 was found to have these same two actions, but the ratio of the phosphate-excretion-effect to the calcium absorption-effect was found to be greater with A T 10 than with vitamin D [Albright, Bloomberg, Drake, and Sulkowitch (1938)].

Since the main action of the parathyroid hormone is to increase phosphate excretion in the urine, it follows that the action of A T 10 more closely resembles that of the hormone than does the action of vitamin D. However, as emphasized by McLean (1941), both A T 10 and vitamin D will raise the serum calcium level in hypoparathyroidism if given in sufficient amounts. Thus whereas theoretically A T 10 is the more suitable preparation to use, when it comes down to a matter of dollars and cents vitamin D is often the drug of choice.

To return to the treatment of hypoparathyroidism, the main indication is to raise the low level of the calcium of the serum to normal without overdoing the process and obtaining hypercalcemia. Thus, all that is needed is an agent to raise the serum calcium and a simple method of gauging this level. A T 10 or vitamin D (see page 127) fills the first need and the Sulkowitch test for calcium in the urine (see page 302) the second.

Once the diagnosis of parathyroid tetany is made, A T 10 is administered in sufficient quantity so that the urine test shows moderate amounts of calcium. If large amounts of calcium appear in the urine, the dosage is reduced and the danger of hypercalcemia is avoided. The patient does

his own tests and modifies the dosage according to the results. The authors usually prescribe about 3 cc of A T 10* a day until calcium appears in the urine and then the dosage is dropped to a maintenance level of about 1 cc three to seven times a week. It is really not necessary to have serum calcium determinations. It must be said, however, that any normal person, shortly after taking a large amount of milk may show an abundance of calcium in the urine. Since one keeps one's patients with hypoparathy-

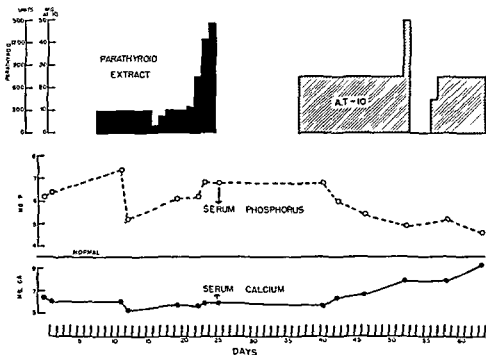


Fig 16 Effect of Parathyroid Extract and Dihydrotachysterol on Serum Calcium and Phosphorus Levels of a Patient with Pseudo hypoparathyroidism

Note that parathyroid extract even in enormous amounts (up to 1500 units per day) was without effect on the abnormal serum calcium and phosphorus levels, whereas large doses of dihydrotachysterol (A T 10) did affect these levels. [From Albright, Burnett, Smith, and Parson (1912)]

roidism on a high calcium diet (*vide infra*), one would expect them always to show hypercalcemia if their levels of serum calcium are normal. Thus it turns out that, if the dosage is reduced when a large amount of calcium is

* Dihydrotachysterol or A T 10 is distributed in the United States by the Winthrop Chemical Company. It is marketed in an oily solution, each cubic centimeter containing 125 mg of dihydrotachysterol. Prior to June 1912 the same preparation was labeled 5 mg per cc because of the presence of then unrecognized inert materials. The preparation is administered by mouth.

noted in the urine, the blood calcium will be kept at a slightly sub normal level. This is probably all the better since it further guards against hypercalcemia and since slight hypocalcemia is not deleterious.

There are a large number of measures other than A T 10 administration which may be useful in the treatment of hypoparathyroidism (Ellsworth (1933)). To be sure, treatment with A T 10 has been so satisfactory that one may be disinclined to bother with the other measures. A few of the salient points will be mentioned. There should be a high intake of calcium and a low intake of phosphorus. Milk, therefore, is contraindicated be-

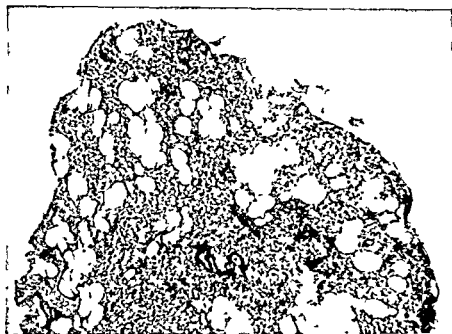


Fig 17 Biopsy of Parathyroid Gland of Patient with Pseudo hypoparathyroidism. Note normal amount of fat tissue which is evidence against a marked degree of hyperplasia. [From Albright, Burnett, Smith, and Parson (1942)]

cause it is high in phosphorus as well as calcium. Dietary conditions are sufficiently met if one omits milk as a beverage from the diet and takes one teaspoonful of calcium gluconate or calcium lactate, dissolved in water, three times a day. One can decrease the phosphate absorption from the gut by administering aluminum hydroxide (one to two teaspoonfuls of a 3-4 per cent preparation three times daily with meals). Just as alkalosis causes tetany, so acidosis tends to alleviate tetany. It is, therefore, helpful in some instances to make the patient slightly acidotic. Calcium chloride by mouth produces a slight acidosis because more chloride is absorbed than

calcium. A favorite prescription in the past has been 10 cc of a thirty per cent solution of calcium chloride diluted in water three times daily after meals. Such a prescription produces a slight acidosis and insures a high

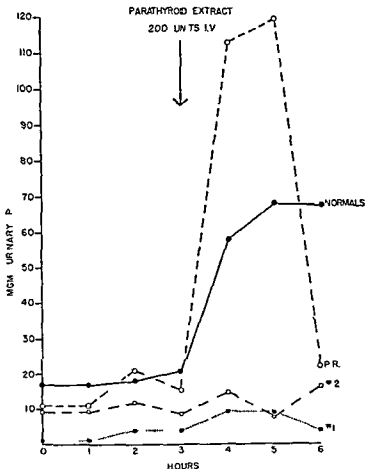


Fig. 18 Effect of Parathyroid Extract Intravenously Administered on the Urinary Phosphorus Excretion in Two Patients with Pseudo hypoparathyroidism Compared with Normal Individuals and Patient P. R. with Idiopathic Hypoparathyroidism [Charted from data in Table I of Albright, Burnett, Smith, and Parsons (1912)]

calcium intake at the same time.* It has been shown that the thyroid hormone tends to raise the serum calcium level in hypoparathyroidism [Albright, Albright, Bauer, and Rosensweig (1932)]. Since many cases of post

* We have some evidence that long continued calcium chloride therapy results in a renal disorder characterized by hypercalcaemia at low serum calcium levels. Until this question is clarified the prolonged use of calcium chloride should be entered upon with caution.

operative hypoparathyroidism are at the same time suffering from a slight thyroid lack it is often wise to push thyroid to the limit of tolerance. Although parathyroid extract has played a large part in the history of parathyroidology it is not used in the therapy of hypoparathyroidism. Its drawbacks are that it is expensive that it often causes a local reaction and that its effectiveness wears out apparently because of anti body formation.

In an acute emergency 10 cc. of calcium gluconate can be administered intravenously this is to be preferred to calcium chloride which often causes thrombosis of the veins and which subcutaneously may cause a slough. It must be emphasized however that whereas the symptoms of tetany may be quite terrifying the condition is seldom fatal. The question has been raised whether there may not be some danger in administering calcium in



Fig. 19 Pseudo hypoparathyroidism Photograph of Three Patients to Show Round Faces

(A) C. M. M. G. H. 14969? (B) I. S. M. G. H. 23993 (cf Fig. 21) (C) R. M. M. G. H. 2876 S (cf Fig. 29) [From Albright, Burnett Smith and Parson (1942)]

patients receiving digitalis. Two cases have been reported in which death ensued apparently from cardiac standstill [Bower and Mengle (1936)].

If the blood calcium is kept normal in hypoparathyroidism cataracts do not develop. Those once formed however do not regress. In many instances their removal is required.

II PSEUDO-HYPOPARATHYROIDISM

This interesting syndrome described by Albright, Burnett Smith and Parson (1942) has essentially the same symptomatology, chemical findings and physical signs as those of hypoparathyroidism but the cause of the disturbance is not a lack of parathyroid hormone but an inability to respond to it. The syndrome has in addition certain developmental abnormalities which serve to delineate it from true hypoparathyroidism.

The identification of the syndrome was the result of a lucky coincidence. The first patient, I S (M G H 239965) a 28 year old female, entered the hospital in March 1940 because of "idiopathic epilepsy" which had been present since the age of 12. Because the bones of the skull by x ray were unusually dense, hypoparathyroidism was suspected. This diagnosis was made when it was found that her Chvostek sign was positive and that her



Fig 20 Pseudo hypoparathyroidism. Photograph of Patient to Show Short Stature

Patient I S (M G H 239965) 28 years old height 137.2 cm (54 inches) [From Albright, Burnett, Smith and Parson (1912)]

serum calcium and phosphorus levels were 6.4 and 6.0 mg per 100 cc respectively. Luckily it was decided, for certain academic reasons, to study the effect of parathyroid extract which is now no longer used in the routine treatment of hypoparathyroidism. She received 74 cc (7,400 units) of parathyroid extract over a period of 12 days without any definite effect upon the serum phosphorus or calcium levels (see Fig 16). It was

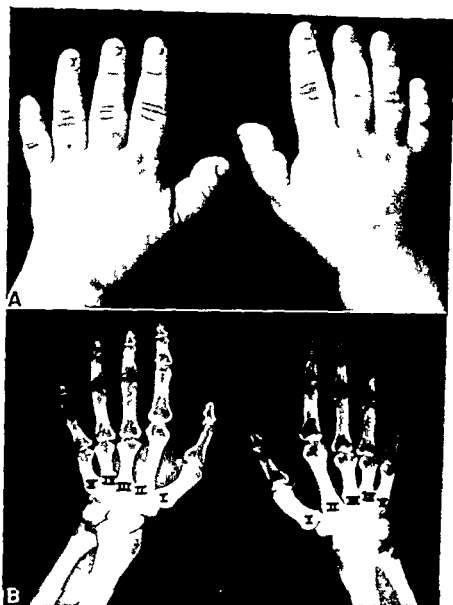


Fig. 91 Pseudo hypoparathyroidism. Photograph and X-ray of hands to show short fingers.

Note the shortness of all fingers except index fingers, the latter being as a result longer than the middle finger. Note that the shortness of fingers is due mostly to short metacarpals. (Patient I S. M.G.H. 23765.) [From Albright, Burnett, Smith and Larson (1912)]

definitely established that she had never received parathyroid extract in the past, so that this amazing resistance to the hormone was not due to anti-

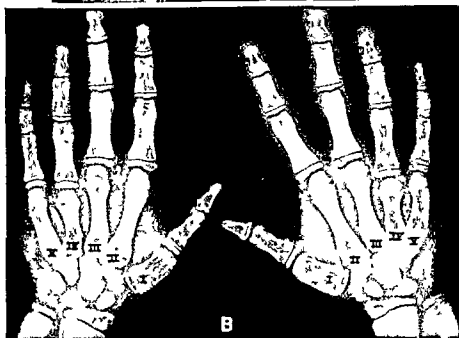


Fig 22 Pseudo hypoparathyroidism Photograph and X ray Film of Hands of Patient of 6½ Years to Show Short Fingers

Note that the epiphyses of metacarpals IV are united and that the epiphyses of metacarpals I and V are in the process of uniting (Patient R M, MGH 28767b)

body formation. Fortunately she did respond well to dihydrotachysterol. The hypothesis suggested itself that, since she was unable to respond to parathyroid hormone, her own parathyroids might not be deficient. She volunteered to undergo an exploration of the parathyroids. Dr. Oliver Cope uncovered the first parathyroid gland looked for, the biopsy of which showed normal parathyroid tissue (see Fig. 17). It was a little surprising that the parathyroid tissue was not hyperplastic, a biopsy on a second similar case did reveal hyperplastic parathyroid tissue.

At the Massachusetts General Hospital there have now been four such cases, three of which were reported in the original publication [Albright, Burnett, Smith, and Parson (1942)]. The authors know of three similar cases: one of Dr. Edmund E. Beard of Cleveland, one of Dr. Randall G. Sprague of the Mayo Clinic, and one of Dr. John S. L. Browne of Montreal.

The resistance to parathyroid extract can readily be demonstrated by the Ellsworth Howard test [Ellsworth and Howard (1934)]. This test is based on the fact that the first metabolic change following the administration of parathyroid hormone is an increase in phosphate excretion in the urine, the test comprises the intravenous administration of 2 cc. (200 units) of parathyroid extract to the fasting subject and the determination of the phosphorus content of urine specimens hourly for three hours before medication and for three to five hours after medication. In Fig. 18 the results in two cases of pseudo hypoparathyroidism are contrasted with those in one case of true hypoparathyroidism and with those in normal individuals.

Albright, Burnett, Smith and Parson (1942), in their first report were struck with a certain sameness in the physical appearance of the patients with this syndrome. Their faces have a tendency to be unusually round (see Fig. 19) and their statures to be thick set and short (see Fig. 20). Thus of the four M. G. H. cases, two were adults (cases 1 and 4) and had heights of 137.2 cm (54 inches) and 152.5 cm (60 inches), respectively. Perhaps the most striking feature, however, is the tendency to brachydactyly, especially as regards the metacarpal bones (Fig. 21 and 22). The cause of the shortness is early closure of the epiphyses (see Fig. 22).

The shortening of the metacarpal and metatarsal bones in pseudo-hypoparathyroidism has been analyzed more closely by Dr. Beard. Short metacarpal bones occurred in our cases 1 and 3, Beard's case, Sprague's case, and Browne's case. If one numbers the metacarpal bones I through V, the metacarpal of the thumb being I and the metacarpal of the little finger being V, it appears from the observations of Pol (quoted by Beard) that these metacarpals are most prone to show shortness which normally begin cartilage proliferation latest and receive their epiphyses latest. For the metacarpals the sequence in order of diminishing lateness of cartilage proliferation and epiphyseal formation is I, V, IV, III and II. The five

cases with short metacarpals mentioned above have adhered pretty well to this order. Thus, Beard's case had all the metacarpals shortened on one hand, and all but metacarpal II on the other, in our case 1 and in Browne's case, all metacarpals were short except metacarpal II on each hand, in Sprague's case metacarpals I, V, and IV were shortened on both hands, the mother of Browne's case had shortening of metacarpals I, V, IV in one hand and of V and IV in the other. In our case 3 (see Fig. 22) it would appear now that he will end with the same distribution of short metacarpals as Sprague's case. Browne's case showed in addition shortening of some of the metatarsal bones and early union of the epiphyses of the bones around the elbow, furthermore, both patient and mother showed bowing of the radius and exostoses such as are seen in dyschondroplasia, these observations suggest that the syndrome under discussion is related to dyschondroplasia.

Browne was impressed with the calcification in certain of the soft tissues especially around the joints. Whereas one meets in true hypoparathyroidism abnormal calcification of the soft tissues, such as calcification of the basal ganglia referred to above, such obvious calcification is apparently not as widespread as in pseudo hypoparathyroidism. Thus, our case 1 showed numerous areas of soft tissue calcification in the extremities, our case 3, a boy of three years and three months, showed areas of calcification of soft tissues of the chest, abdomen, and extremities, some of which could be felt on physical examination.

Great interest is attached to Browne's case since the mother likewise had abnormalities of the metacarpal bones. Unfortunately, there has been no opportunity as yet to establish the presence of pseudo-hypoparathyroidism in the mother.

CHAPTER 3

CLINICAL HYPERPARATHYROIDISM

I PRIMARY HYPERPARATHYROIDISM

(A) *Definition*

By "primary hyperparathyroidism" is meant a condition where more parathyroid hormone is manufactured than is needed. By "secondary hyperparathyroidism" is meant a condition where more parathyroid hormone is manufactured than is normal but where this hormone is needed for some compensatory purpose.

(B) *Etiology*

Primary hyperparathyroidism may be due to a single adenoma or a carcinoma of one of the four glands, to multiple adenomata, or to hypertrophy of all parathyroid tissue. In the first fifty cases of hyperparathyroidism proved by operation or autopsy at the Massachusetts General Hospital there were forty-one cases of single adenomata, three cases of two adenomata, and six cases of hypertrophy.

The cause of the adenomata is, of course, unknown. It is of interest, however, that six per cent of this series of cases had two adenomata, two glands being involved. This, of course, suggests that the predisposing factor to adenoma formation must at some time have affected all parathyroid tissue. It seems not improbable that a preexistent hyperplasia of the parathyroids may be this predisposing factor. Indeed, Erdheim (1907) has described "germinative centers" in hyperplastic parathyroid gland. It may well be that one or more of these centers occasionally lose their property of being controlled by normal stimuli and turn into adenomata producing hormone regardless of the bodily needs. The question, therefore, arises whether there is any evidence that hyperparathyroidism occurs in patients who have had a preexistent hyperplasia of the parathyroid glands.

There are four well recognized conditions in which one encounters hyperplasia of the parathyroid glands, namely rickets (or osteomalacia), pregnancy, renal insufficiency of the type associated with phosphate retention and calcium deprivation. All of these four conditions have a tendency to a low serum calcium value and it seems not improbable that the normal stimulus to parathyroid hormone production is a serum calcium value below normal.

If pregnancy is a factor, one would expect to find more cases in females than in males. Such seems to be the case. Thus of the first 83 proved cases at the Massachusetts General Hospital, 55 were females and 28 males.

In 1934 when the Massachusetts General Hospital cases stood at 18 proved cases one of the authors was able to collect from the world literature 82 cases making 100 cases in all of these 69 were females and 28 males in three the sex was not reported. The increased incidence in females therefore may suggest that the hyperplasia of the parathyroids during pregnancy is a factor. One case in the authors experience is of special interest in this respect. The patient had developed a tumor of the neck following a miscarriage fourteen years before admission. This tumor of the neck later proved to be a parathyroid adenoma and the cause of her presenting symptoms.

In cases where one finds multiple adenomata in one patient the explanation may be that a preexisting hyperplasia led to multiple germinative centers and hence to multiple adenomata. In a few instances a second adenoma seems to have developed after removal of the first. We have no data to show whether the second adenoma was already present at the time of the first operation and merely enlarged thereafter or whether it originated after the first operation. If the second explanation is the correct one it would be evidence in favor of some continued influence making for adenomata formation. The authors prefer the first explanation.

The authors are not aware of any clinical evidence which definitely links hyperparathyroidism with a preexisting rickets. There is apparently no increase in incidence in the colored race contrary to what one would expect if this were true.

There is perhaps some correlation between the incidence of hyperparathyroidism and the history of a low calcium intake. Marine (1913) found enlargement of the parathyroid glands in fowls on a low calcium diet. Luce (1923) confirmed this in rats. Pierre de Boissezon and Lombard (1939) found that sodium phosphate injections in rabbits and dogs caused parathyroid hyperplasia whereas calcium gluconate injections decreased the size of the parathyroid. Finally Ham Littner, Drake, Robertson and Tisdall (1940) found hypertrophy of the parathyroid glands in rats made rachitic on a low calcium high phosphorus regimen but not in rats made rachitic on a high calcium low phosphorus regimen. Several patients with hyperparathyroidism have given a history of a long continued calcium deficient diet. Thus the sea captain first studied by Hannon Shorr, McClellan and DuBois (1930) had been on a diet almost devoid of milk, eggs and green vegetables. Wilder's (1929) patient had always avoided milk, cream and vegetables. This interestingly enough, had been brought out by Dr. George R. Minot of Boston who had studied the patient because of her anemia. The authors are aware of other patients who have had an unusual dislike for milk.

In summary therefore it seems possible that parathyroid adenomata

formation may be connected with the following sequence of events (A) some situation tending to lower the serum calcium level (B) stimulation of all parathyroid tissue (C) formation of many circumscribed "germinative centers", and (D) loss on the part of one or more of these centers of their property of being controlled by normal stimuli.

There is some evidence that pituitary hormones and insulin may play a part in the causation of parathyroid tumors and hyperplasias. Houssay (1936) showed in dogs that pituitary insufficiency is associated with an atrophy of the parathyroids, which, however, is not accompanied by any change in the serum calcium level and that anterior pituitary extract can increase the size of the parathyroids. Hertz and Krane (1934) induced hyperplasia in rabbits with similar extracts. The observation of Cattleman and Hertz (1939) of marked depletion of the cells of the parathyroids in a case of panhypopituitarism has already been mentioned (see page 27). Houssay further showed that in pancreatic insufficiency in the dog there is protoplasmic disintegration of parathyroid tissue, this time associated with a fall in the serum calcium level and a rise in the serum phosphorus level; he found in addition that insulin prevents the fall in serum calcium.

Erdheim (1903) was one of the first to describe the finding of enlarged and even adenomatous parathyroids in conjunction with eosinophilic pituitary tumors and acromegaly; in his case the largest of the parathyroid glands measured $1.7 \times 0.6 \times 0.3$ cm. Others to report similar findings in acromegaly include Claude and Baudouin (1911) and Cushing and Davidoff (1927a). Schmorl (1912) [see also Molineux (1913)] reported the finding at autopsy of a large basophil tumor of the pituitary together with adenomatous enlargement of the parathyroid glands and *ostitis fibrosa generalisata*.

Special interest is attached to those cases in which in addition to pituitary and parathyroid tumors there are one or more co-existing pancreatic islet tumors. Lloyd (1929) reported adenomatous enlargement of two out of three parathyroid glands in a patient dying with a chromophobe pituitary adenoma without evidence of acromegaly; the patient had in addition, adenoma-like enlargement of the islets of Langerhans and moderate enlargement of the adrenals and ovaries. Shelburne and McLaughlin (1945) reported a similar case with clinical evidence sufficient to make a diagnosis of pituitary tumor in whom hyperinsulinism was first relieved by removal of three islet tumors and hyperparathyroidism was subsequently relieved by removal of one parathyroid adenoma. This academically most interesting but as yet inexplicable interrelationship between pituitary, parathyroid and islet tissues was brought to the authors' attention by our colleagues at the Mayo Clinic [Kepler, Ryncarson, Sprague and Keating (1947)]. They have under observation two cases of hyperparathyroidism with marked parathyroid hyperplasia associated with islet and pituitary

tumors In the Massachusetts General Hospital series of 89 proved cases of hyperparathyroidism, no case with an associated pituitary or islet tumor has been found We have one case of acromegaly who has a high serum calcium level and a normal rather than high* serum phosphorus level on whom we have made the secondary diagnosis of hyperparathyroidism, unfortunately, however, she refuses operation

(C) Parathyroid Pathology

(1) Normal Histology

Under low power magnification parathyroid tissue from the normal adult with its islands of epithelial cells dispersed with fat cells looks not unlike bone marrow The fat cells however, do not appear in the stroma until after puberty, thereafter they increase in number until about the age of forty The epithelial cells consist of two main types the chief cell and the oxyphil cell The chief cell is 6 to 8 microns in diameter with a *large nucleus from 4 to 5 microns in diameter* Its cytoplasm with the hematoxylin and eosin stain may have a pinkish or a partially vacuolated or an entirely vacuolated appearance if the last it is spoken of as a 'water clear' or 'wasserhelle' chief cell This type of chief cell tends to be somewhat larger than those in the group as a whole since its cell membrane is very distinct, it has been likened unto a plant cell The oxyphil or Welsh cell differs from the chief cell in having a reddish granular cytoplasm and in being somewhat larger, 11 to 14 microns Most authors distinguish between a pale and a dark oxyphil cell the latter has a much smaller nucleus which is intensely pyknotic, and a more darkly red cytoplasm

The distribution of these various cells varies with age Oxyphil cells do not appear until after puberty but thereafter they increase with age They do not contain fat or glycogen The chief cells contain both glycogen and fat, the latter, however, does not appear until soon after puberty or cessation of growth The epithelial cells form cords and occasionally follicles After puberty the latter may contain colloid giving an appearance not too unlike thyroid tissue to the untrained microscopist

For a further discussion of normal histology in the English language the reader is referred to Castleman and Mallory (1935)

(2) Adenomata (Parathyroidomata†)

The adenomata vary in size from structures which are smaller than the normal parathyroid gland to tumors several inches in diameter, which are

* The serum phosphorus level tends to be high in acromegaly [Reifenstein Hill and Albright (1946) see page 188]

† At times this type of tumor is more properly called a parathyroidoma rather than an adenoma because the cells do not form glands [Castleman (1945)]

clinically easily demonstrable. With the smaller tumors it is quite often possible to find a crescent of normal parathyroid tissue on the outside of the tumor (see Fig. 23). Since the adenomata, as a rule, consist of solid masses of epithelial cells, the remaining rim of normal parathyroid tissue can easily be recognized because of the interspersions of fat cells. The cell type in functioning adenomata is apparently invariably the chief cell. It is the opinion of Castleman and Mallory that the oxyphil cells are non-functioning cells and that parathyroid cells to function must contain glycogen. For a more thorough discussion of the histology of the adenomata the reader is referred to Castleman and Mallory (1935). The most important clinical consideration, of course, is to be able to differentiate at operation this type of pathology from hyperplasia and from hypertrophy. The



Fig. 23. Photomicrograph of Parathyroid Adenoma from Patient with Mild Hyperparathyroidism (M. G. H. 312120)

A—parathyroid adenoma, B—crescent of normal parathyroid tissue

differentiation will be discussed below under "Hypertrophy of the Parathyroids." Hypertrophy and Hyperplasia of the Parathyroids" (*vide infra*)

(3) Carcinomata

The authors are aware of only three cases in which unquestionable cancer of the parathyroid glands was associated with hyperparathyroidism [Gutman (personal communication), Meyer, Ross, and Ragins (1939) and Gentile, Skinner, and Ashburn (1941)] * Dr. Alexander B. Gutman of the Presbyterian Hospital in New York City was kind enough to supply some

* Since this manuscript was prepared a female patient (M. G. H. 602541) with cancer of the parathyroids has been referred to Dr. Oliver C. Peck, Dr. R. M. Hurten of Racine, Wisconsin. This patient constitutes case number 89 in our series of proved cases of hyperparathyroidism.

of the interesting details of one of these cases. The patient underwent a parathyroidectomy in July, 1938 at the age of 56 for what appeared to be classical hyperparathyroidism with osteitis fibrosa and an elevated serum calcium level (19.6 mg %). At operation a parathyroid tumor 1.5 cm in length was found because the tumor was invading the blood vessels, the adjacent thyroid gland, and the capsule, it was considered to be carcinomatous. The patient made a spectacular recovery with recalcification of the skeleton and a return of the serum calcium level to normal. However, in October 1940 he had a recurrence of hyperparathyroidism and of the clinical, x-ray, and chemical findings. A second exploration revealed several masses of carcinomatous tissue.

Castleman (1945) was unable to find a single example of parathyroid carcinoma in more than eighty tumors of the parathyroid glands. It is therefore apparent that the criteria for the diagnosis of malignancy must have been quite different, and we think questionable in the series of cases reported by Alexander, Pemberton, Kepler, and Broders (1944), in which they found thirteen 'carcinomata' out of fourteen cases.

(1) Hypertrophy of the Parathyroids? Hypertrophy and Hyperplasia of the Parathyroids?

The condition which the authors now call 'hypertrophy of the parathyroids' is most interesting and apparently rare [Albright, Sulkowitch and Bloomberg (1938)]. Although it has occurred in 8 cases in the Massachusetts General Hospital series of 89 proved cases of hyperparathyroidism, no similar instance of the diagnosis having been made during life had been reported from other clinics of this country up to 1947*. The condition involves all parathyroid tissue and was first considered to be hyperplasia and was so designated in a publication by one of the authors and his colleagues [Albright, Bloomberg, Castleman, and Churchill (1934)]. Castleman and Millory (1935) designated the condition "primary hyperplasia" as opposed to "secondary hyperplasia".

The composite weights of the four glands of the first 6 cases with this condition of the Massachusetts General Hospital series varied from 2.510 mg. to 19,100 mg., values which are roughly 20 to 160 times the mean weights of normal glands. Gilmour and Martin (1937) found that the means and standard deviations of the weights of normal parathyroid tissue are 117.6 and 45.97 mg. respectively, for men and 131.3 and 15.02 mg. for women. The smallest set of glands in their series weighed 25 mg. and the largest 388 mg.

* In February 1947 Black and Sprague (1947) reported a classical example of this condition diagnosed at operation and treated by subtotal resection. This was case 50 of the Mayo Clinic series of patients with primary hyperparathyroidism.

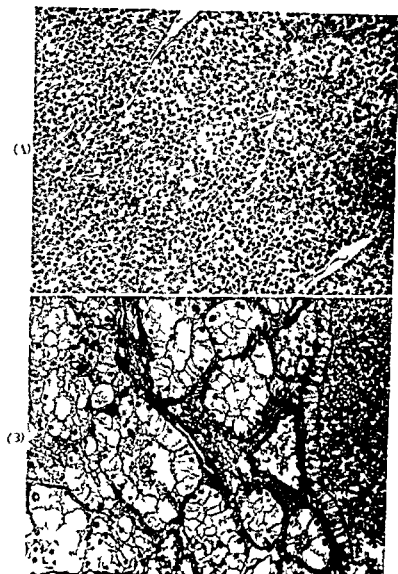


Fig. 21 Photomicrographs to illustrate the difference in parathyroid histology between (A) Hyperplasia Secondary to Renal Insufficiency and (B) Parathyroid Hypertrophy

Note tremendous difference in size of parathyroid cells. (A) is taken from Case No. 9 see page 118. [From Albright, Drake and Sulkowitch (1937)]

The histology (see Fig 24B) in all 6 cases and in all glands from any one case was exactly the same. Furthermore, it was absolutely different from that seen in any other condition. The parenchymatous cells resembled the normal wasserhelle cells except that the characteristics that differentiate a wasserhelle cell from the usual chief cell were very much intensified. Whereas a normal chief cell varies in diameter from 6 to 8 microns and a wasserhelle chief cell is somewhat larger 8 to 10 microns, these cells were very much larger, 10 to 40 microns. Furthermore, the cytoplasm was absolutely water clear and there was a marked tendency for the cells to arrange themselves in alveolar formation.

It would seem to the authors that, as pointed out by Albright, Sulkowitch and Bloomberg (1938), the parathyroid pathology may consist merely of a ballooning out of the cytoplasm of the cells. Thus, by rough measurement, the diameters and hence the radii are of the order of magnitude of three to five times that of a normal chief cell. Since the volume of a sphere increases as the cube of the radius, a four fold increase of the radius would cause a sixty four fold increase in the volume. It will be seen that this again is of the order of magnitude of the actual increase in the size of the glands. Against the condition being a hyperplasia is the fact that it in no way resembles the pathology seen in cases where there is known hyperplasia (e.g. in secondary hyperparathyroidism), where the cells are normal or only slightly increased in size (see Fig 24A).

Rogers and Keating (1947) reviewed 22 cases of this condition from the literature and added 4 cases from the Mayo Clinic. They conclude that the parathyroid pathology cannot be explained by hypertrophy alone. In the first place, they point out that the weight of the four glands of one of their four patients was three grams and that of another 54 grams and that accordingly, on the basis of the figures for mean parathyroid weights of Gilmour and Martin (1937), these two sets of glands were 26 and 410 times normal, respectively. From their measurements of cell size on the other hand, they conclude that the mean volume of the cells in this condition is only 27 times normal and that hence only the smaller set of glands could be explained by hypertrophy alone. We grant that this conclusion is irrefutable if the measurements are not in error. The estimation of the size of cells is admittedly a difficult task. In the second place Rogers and Keating point out that the mean diameter of the parathyroid cells in the condition under discussion is 20 to 21 microns regardless of the composite size of the parathyroid gland. They speculate that if hypertrophy alone, and not hyperplasia, were the cause of the enlargement, one would expect a much greater mean cell diameter in the larger set of glands. To this part of the argument the authors do not subscribe since the figures of Gilmour and Martin (1937) (*vide supra*) show a marked range in the size of sets of normal

parathyroids (25 mg to 388 mg) In conclusion we feel that whereas the case for hypertrophy has by no means been proven it has not been altogether refuted *

In the original communication describing this condition [Albright Bloomberg Castleman and Churchill (1934)] considerable circumstantial evidence was presented which suggested that the condition might be secondary to an excess of some pituitary parathyrotrophic substance Careful study of these cases however has supplied no evidence to confirm this hypothesis It seemed possible that the extraordinary enlargement of these cells might be due to a storing of parathyroid hormone If such were the case one would expect a gram of parathyroid tissue from one of these individuals to contain more hormone than a gram of parathyroid tissue from a normal individual Dr J B Collip was kind enough to carry out a biologic assay on some of this tissue and found no appreciable deviation in the hormone content from that of normal tissue

Thus the nature of this interesting condition remains entirely obscure

(D) *Clinical Findings in Primary Hyperparathyroidism*

The clinical findings in hyperparathyroidism can be divided into three headings (1) those due to bone disease (2) those due to disease of the urinary tract and (3) those due to hypercalcemia *per se* One perhaps should add a fourth category namely findings due to decreased hematopoietic function

(1) *Skeletal Disease in Primary Hyperparathyroidism*

As will be discussed in more detail below it is a mistake to think of bone disease as an essential part of hyperparathyroidism In many cases there is very severe hyperparathyroidism and no bone disease at all It so happens that cases with bone disease played an important part in the early history of hyperparathyroidism and have made a lasting impression on most people's minds The bone disease when it does occur consists of a generalized decalcification with superimposed cysts and tumors and is designated osteitis fibrosa generalisata of von Recklinghausen or osteitis fibrosa cystica The terminology is not all that could be desired but it would be a mistake to attempt to make changes at this late date Osteitis is of course misleading since this condition is not an inflammation Fibrosa calls attention to one of the most striking features of the histology namely an increase in the supporting cells of the bone marrow These cells it has

* Dr Robert H Fernell Jr of the Dept of Pathology made a careful study of our eighth case with the following comments in which he used as an index of the size of the cells the number of nuclei per microscopic field He concluded that the condition could not be explained by hypertrophy alone to this conclusion the author bows

been suggested, give rise to osteoblasts and osteoclasts and, since both these latter two cell types are increased, it is perhaps not surprising to find an increase in the parent cell type. The authors prefer "generalisata" to "cystica." "Cystica" calls attention to the fact that some cases have superimposed cysts filled with fluid and lined with fibrous tissue, these cysts are almost certainly degenerative phenomena. A good many cases however, do not have cysts. "Generalisata" emphasizes the fact that the bone condition is generalized as is true of most metabolic diseases. This is a very important differential point in distinguishing bone disease of hyperparathyroidism from certain other conditions (*vide infra*). Von Recklinghausen's name is usually appended because it has been believed that he described three examples of this condition in 1891. As a matter of fact the authors now believe that two of his three cases had an entirely different condition, polyostotic fibrous dysplasia (see page 283).

Bone tumors, which are commonly present in the bone disease associated with hyperparathyroidism, are not as a rule referred to in the descriptive name of the disease. They consist of solid masses of soft tissue without bone, composed of the supporting cells of the bone marrow, osteoblasts, and osteoclasts. Hunter and Turnbull (1931) designated them as "osteoclastomata." In the authors' opinion "osteoblastomata" would be equally suitable except that an osteoclast is a more imposing looking cell than an osteoblast.

All degrees of skeletal decalcification are met with clinically from the patient with no bone changes to the patient with practically complete loss of skeleton, dying of inability to raise his thorax in respiration. The early symptoms may be indefinite pains which too often are attributed to "rheumatism", "arthritis", or "neuritis". Bone tenderness is a very constant feature. Surprising is the rapidity with which it disappears after removal of the tumor whereas it may take months for enough calcium to be deposited to show by x ray. This feature is well illustrated in Mandl's historic case (1926) of a Viennese street car conductor. He states "The present illness began five years ago with a from day to day increasing tiredness and feeling of pain in the pelvis and lower extremities. The pains were increased by all bodily efforts sneezing, coughing, defecation, et cetera. In the course of months the suffering so increased that the patient had to be pensioned." The patient was successfully operated upon in July, 1925 (world's first parathyroid exploration!) and by the end of August the pains in the extremities were reduced to a minimum.

All kinds of bone deformities, of course, occur. These include bending of the long bones, deformities of the pelvis similar to those seen in osteomalacia, and various deformities of the vertebrae ("fish bone vertebrae") crushed vertebrae, and herniations of the nuclei pulposi through the

plates of the vertebrae—so-called "schmorlsches Knötchen"; see Fig. 56, p. 118 and Fig. 70, p. 141). A characteristic result of the vertebral changes is a decrease of stature, a "pigeon-breast" deformity of the chest, and a disappearance of the neck into the thorax (see Fig. 25). It must be said, however, that the bones in this disease are more brittle than in osteomalacia so that fractures rather than bending is the rule.

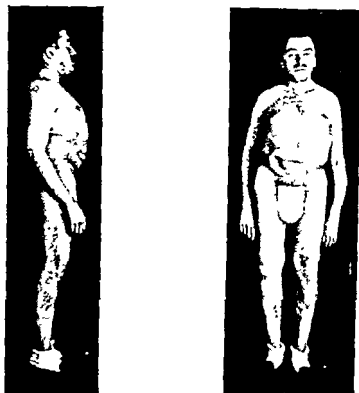


Fig. 25. Captain Charles Martell, Historic Patient with Osteitis Fibrosa Generalisata

Note short neck and pigeon breast deformity due to collapsed vertebrae.

Perhaps it will be of value and interest to cite at this point a few excerpts from the history of DuBois' now famous patient and mariner, Captain Charles Martell [Hannon, Shorr, McClellan, and DuBois (1930); Bauer, Albright, and Aub (1930); and Bauer (1933)] "In November 1918, when 22 years old, he slipped and felt a sharp severe pain in his right loin which lasted one week. Three months later pains were felt in legs and hips and became more severe and extended upward to the lumbar spine. About July, 1919 a fellow officer noted that he was growing shorter and becoming pigeon-breasted. The neck shortened and thickened so that he had to wear

larger collars Pains in the heels, legs and back were caused by the jars of walking and coming downstairs "

Besides the bone symptoms due to generalized decalcification are those due to bone tumors and cysts. Clinically, for the time being, these two must be discussed together. Both lesions by x ray are characterized by an absence of bony structure and hence are very similar in appearance, they are both apt to be called 'cysts'. They give rise to symptoms either by producing tumors or by causing pathological fractures. It is distressing how often the sequence of events is appearance of a bone tumor, biopsy, diagnosis of benign giant cell tumor, local treatment, and finally recognition of generalized disease only years later. Thus in Beck's case (1928) the lower leg was amputated in the belief that the tumor was malignant. Nine years later the correct diagnosis was made and a parathyroid tumor was removed. Tumors occur in certain areas of predilection—notably jaws, metacarpals and metatarsals, and ends of long bones. Several cases in the Massachusetts General Hospital series were picked up by the Dental Department. Whereas every case of epulis is certainly not hyperparathyroidism, this diagnosis must be carefully considered in such a case.

A *Roentgenographic Diagnosis of Osteitis Fibrosa Generalisata*

The roentgenographic diagnosis of osteitis fibrosa generalisata offers little difficulty. One looks for generalized decalcification. As evidence of this it is often helpful to know whether or not the lamina dura is still visible around the teeth. If it is not, the inference is that general decalcification is present [Strock (1941), see Fig 26]. Especially characteristic is the even ground glass appearance of the skull, which, in the authors' experience, is not met with in any other condition except renal osteitis fibrosa generalisata or renal rickets (*vide infra*). The thickness of the skull is not affected (see Fig 27). One looks for cysts and tumors. Both of these appear on x rays as cysts. Furthermore, an area of fibrosis where the bone trabeculae are mostly destroyed will also appear cystic. The authors refer to these as "pseudo-cysts". The correct interpretation of the underlying lesion in some cases must be deferred until after the hyperparathyroidism has been cured, when the true cysts will remain as cysts, and the "pseudo-cysts" and tumors will turn into solid bone (see Fig 53, p 113). A cortical "cyst" is most suggestive of hyperparathyroidism. The teeth fail to show any decalcification and therefore contrast markedly with the decalcified bones of the face (see Fig 26C). The differential diagnosis between osteitis fibrosa generalisata and other bone diseases will be discussed below.

(2) Clinical Findings Associated with the Urinary Tract

The symptomatology associated with the urinary tract may be divided into three parts (A) that due to hypercalcaemia and hyperphosphaturia,

(B) that due to the formation of kidney stones, and (C) that due to calcium deposits in the kidney parenchyma

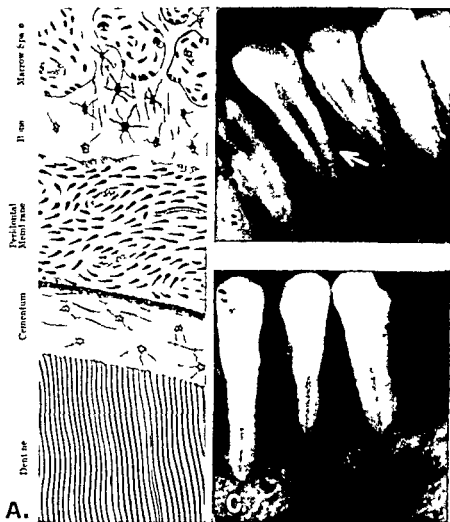


Fig. 2. Illustration to show absence of lamina dura in hyperparathyroidism with bone disease

A—Drawing from Stroock (1911) showing relation of lamina dura to structures about teeth. B—X-ray film of teeth from normal individual; arrow indicates lamina dura. C—X-ray film of teeth from patient with hyperparathyroidism with bone disease showing absence of lamina dura.

Marked polyuria and polydipsia are usually associated with the hypercalcaemia and hyperphosphataemia of hyperparathyroidism. If one administers parathyroid hormone to a normal individual, one obtains for a short

while an increased excretion of water, inorganic base, and chloride, similarly with cessation of hormone administration these same three substances are withheld in the body [Albright, Bauer, Ropes, and Aub (1929), Illworth and Nicholson (1935)] Almost all patients with hyperparathyroidism have a marked oliguria immediately following the successful removal of a parathyroid adenoma. In some instances it may be sufficient to cause alarm. Thus, Snapper's patient (1929) excreted two liters of urine daily before the operation, 800 cc on the day of the operation, but only 150 cc on the day after the operation, the N P N rising from 31 mg to 55 mg.

Because of the polyuria and polydipsia, several cases of hyperparathyroidism have been faultily diagnosed as diabetes insipidus. There is, however, another cause for polyuria in patients with hyperparathyroidism, namely, tubular damage. This may occur in association with nephrocalcinosis (*vide infra*), but also without demonstrable nephrocalcinosis by x ray. Case No. 1 which follows illustrates this point and indicates that a certain degree of renal damage is reversible.

Case No. 1 Hyperparathyroidism Simulating Diabetes Insipidus Secondary Anemia

Mrs. P. G. (M. G. H. 589), a spinster of 59, entered the Metabolic Ward in September 1941 for investigation of her water balance and for verification of the diagnosis of hyperparathyroidism.

Five years previously, while at the Massachusetts Eye and Ear Infirmary for a radical mastoidectomy, it had been noticed that she had a large fluid intake (4-7 liters daily), routine urine analysis at that time had been normal. Two years previously she had been seen in the Outpatient Department complaining of fatigue and sleepiness. At that time she had had some ankle edema, a blood pressure of 160/100 mm. of mercury, a phenolsulphonphthalein excretion of 5 per cent in 15 minutes with a total of 25 per cent in the first hour, and a hemoglobin of 8.4 gm. per 100 cc.

She was studied on the Medical Service two months before the present admission because of polyuria, polydipsia, and hypertension (150/100 mm. of mercury). Studies revealed an inability to concentrate. Thus urinary specimens taken at random showed specific gravities varying from 1.001 to 1.010, repeated urine concentration tests including one in which the patient received 10 International Units of pituitrin resulted in gravities up to 1.010 only, except for one isolated reading of 1.014. The urine contained no albumin and the urinary sediment was normal, the urine pH varied from 5.5 to 6.5. The serum non-protein nitrogen and protein levels were normal, the serum CO₂ content was 25.5 m. eq. per liter, the serum chloride 111.4 m. eq. per liter, the serum calcium 12.4 and 12.3 mg. per 100 cc., the serum phosphorus 2.4 and 2.7 mg. per 100 cc., and the serum alkaline phosphatase 1.6 and 1.9 Bodansky units. The 24 hour urinary calcium excretions while on a low calcium intake were 94 mg., 105 mg., and 92 mg., on three successive days. The red count was 3.6 million and the hemoglobin 7 gm., these values responded to iron therapy. Two phenolsulphonphthalein excretion tests showed values essentially as previously. An intravenous pyelogram revealed normal

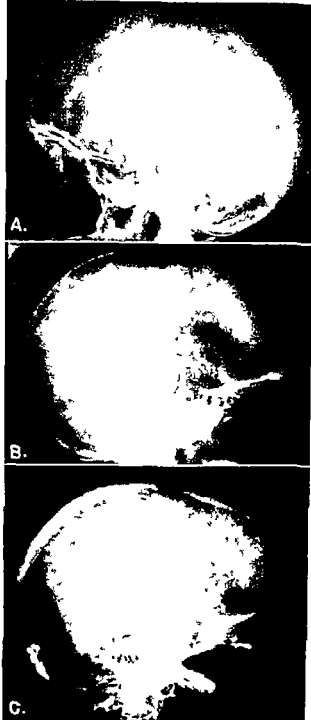


Fig 27 Illustration to Contrast X ray Appearance of Different Types of Skulls
 A—normal skull, B—thin "moth eaten" skull of osteitis fibrosa generalisata (pt
 M G H 327943), C—thick, "moth eaten" skull of osteitis fibrosa generalisata (pt
 M G H 310023), D—thin, well-calcified skull of osteogenesis imperfecta E—over

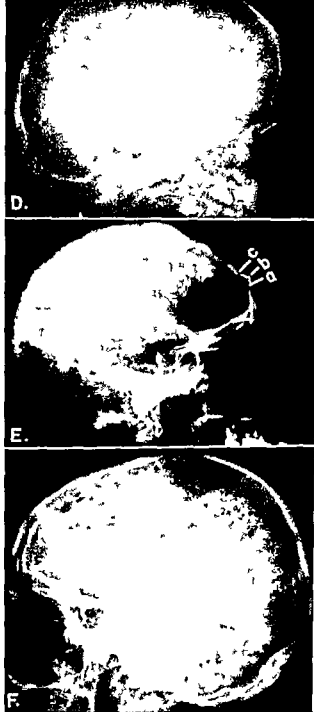


Fig 27 (continued)

grown fuzzy skull of Paget's disease F—skull of multiple myeloma peppered with sharply punched out areas (Note furthermore, in Paget's disease skull (E) transition from normal bone to Paget's disease, a—end of normal bone, b—zone of increased bone destruction c—beginning of overgrowth of bone)

appearing kidneys prompt excretion of rather dilute dye and a questionable stone lay down in the course of the right ureter

Studies on the Metabolic Ward confirmed the previous findings except that the red count had risen to 5.6 million and the hemoglobin to 11 gm. The specific gravity of the urine varied from 1.001 to 1.010, most values being 1.005. Kidney function tests carried out by Dr. John H. Talbott showed a glomerular filtration *circa* 50% of normal, a renal blood flow *circa* 60% of normal and a maximum capacity of the tubules to secrete diodrast *circa* 66% of normal.

On November 7, 1941 Dr. Oliver Cope removed a parathyroid adenoma. One week later the serum calcium had fallen to 10.9 mg. and the serum phosphorus had risen to 3.6 mg. per 100 cc.

The most interesting question was whether the inability to concentrate represented a structural tubular damage or a functional disorder resulting from the high parathyroid hormone level. If the former, it should continue after the operation; if the latter, it should immediately disappear. A urine concentration test carried out one week after the operation showed a specific gravity of only 1.006. A second concentration test in which pituitrin was administered showed a gravity only up to 1.012. Dr. John Talbott repeated his tests after the operation with essentially the same findings. The hemoglobin 23 days after operation had risen to 14 grams per 100 cc.

The patient's condition was re-evaluated one year after the operation. She still had hypertension (170/100 mm. of mercury). Her serum chemistry was normal except for a slightly high chloride level (111 m. eq. per liter) and a slightly low CO_2 content (24 m. eq. per liter). Her phenolsulphonphthalein excretion had risen to 25 per cent in 15 minutes and 40 per cent in one hour. She concentrated up to 1.018 after receiving one half cc. of surgical pituitrin. Her hemoglobin was 15 and 14.1 gm. per 100 cc.

In summary, therefore, we have a patient with proved primary hyperparathyroidism without bone disease, who developed hypertension and definite renal impairment including marked hyposthenuria without demonstrable nephrocalcinosis or proven nephrolithiasis. After the removal of the parathyroid adenoma she showed improved kidney function, not immediately but at the end of one year. The patient also had a secondary anemia which was partially relieved by iron therapy and which was totally relieved by removal of the parathyroid adenoma.

Nephrolithiasis is a common complication of hyperparathyroidism, it, or nephrocalcinosis, or both, occurred 52 times in the first 64 cases studied at the Massachusetts General Hospital, in the same series of cases bone disease occurred only 35 times.

Since the cause of the stones is presumably the hypercalcemia, one would expect calcium phosphate and possibly calcium oxalate stones. Such seems to be the case. Since the ratio of calcium to phosphorus in tertiary calcium phosphate is 2 to 1, and since there is no phosphorus in calcium oxalate, one would anticipate a ratio of 2:1 or greater in stones from patients with hyperparathyroidism. Where the cause of stones is an alkaline urine, one would anticipate as ingredients of the stones not only calcium phosphate

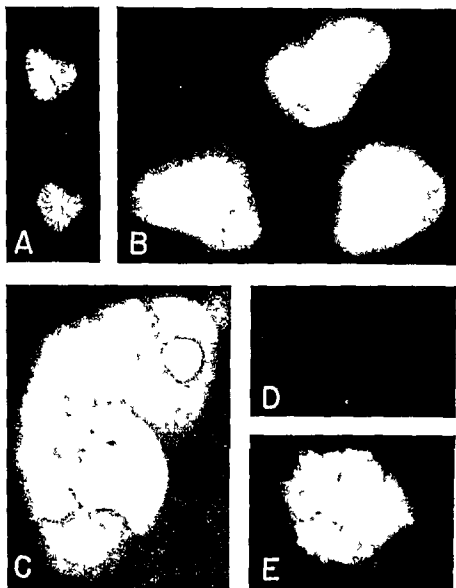


Fig 28 X ray Appearance of Typical Kidney Stones

(A) Oxalate stones note crystalline structure and tendency to be triangular (B) Three phosphate stones of same patient note characteristic ring formation and note that same rings occur in each stone (C) Cystine stones note homogeneous structure and tendency for small stones to amalgamate into larger stones (D) Uric acid stone note that you see nothing! (E) Oxalate stones, the so called jackstone variety

but also magnesium ammonium phosphate, thus, the ratio of calcium to phosphorus would be less than 2:1 and the stone would contain magnesium as well. Actual analysis confirms the above speculations, except that one

must remember that one may have the following sequence (a) hyperparathyroidism (b) pure calcium phosphate stones (c) infection (d) alkaline urine and (e) a coating of the stones with a mixture of magnesium ammonium phosphate and calcium phosphate



Fig 29 Photomicrograph of Kidney Tissue of a Rat Which Had Received an Overdosage of Parathyroid Extract

Calcium casts can be seen in tubules. Black spots represent calcium deposits (Van Kossa's stain). [From Allright and Bloomberg, (1934)]

It is becoming increasingly important that the chemistry of stones be recognized in order that the correct medical treatment can be applied. This can frequently be done by the x-ray appearance. Calcium oxalate stones have a crystalline structure with radiations from a central point (see Fig 28). phosphate stones with or without magnesium grow in size by concentric layers. cystine stones are homogeneous and sometimes grow by

many smaller stones being fused together, finally, uric acid stones are not discernable by x ray. Only phosphate and cystine stones can be staghorn in structure. There are, of course, mixed stones such as a stone with an oxalate center and a phosphate cortex, the sequence of events in such a case is (1) oxalate stone, (2) urinary infection (3) alkaline urine, and (4) phosphate coating to the oxalate stone.

The passing of calcium phosphate sand is also a frequent symptom. The symptomatology secondary to the kidney stones will not be discussed.

A much more serious complication of hyperparathyroidism is the formation of calcium deposits in the collecting tubules of the kidney,—so called nephrocalcinosis. In the authors' experience the patients who have nephrocalcinosis usually do not have nephrolithiasis and *vice versa*. The pathology of nephrocalcinosis is apparently is a plugging of the tubules with calcium casts (see Fig 29). In patients with this condition one not infrequently sees calcium phosphate casts in the urinary sediment. These casts are not pathognomonic of hyperparathyroidism since they occur commonly in any alkaline urine from a normal individual provided that the urine contains a large amount of calcium and phosphate, such would be the case if the individual is a "milk drinker". These casts disappear when the pH of the urine becomes more acid than 6.1 [Albright and Bloomberg (1934)].

(3) Clinical Findings Due to Hypercalcemia *Per Se*

Just as hypocalcemia causes increased excitability of the nerve muscle apparatus and tetany, so hypercalcemia causes decreased excitability. This can be demonstrated by the electrical reactions. Thus, Hannon Shorr, McClellan, and DuBois (1930) found decreased electrical reactions in their historic patient, about twice the amount of current being required to excite a nerve as normally. The hypercalcemia manifests itself in the electrocardiogram by a shortening of the Q-T interval (i.e. short ventricular systole) although the length may still be within normal limits [Kellogg and Kerr (1936), Graybiel and White (1941)].

Many observers have been struck with the hypotonicity of the muscles. This was especially marked in the patient reported by Barr and Bulger (1930) (see Fig 30), who could do contortionist tricks. General muscular weakness is frequently present and is presumably the subjective expression of the more objective hypotonicity. The lack of tone also involves smooth muscles and leads to a variety of symptoms such as constipation, poor appetite and so forth. A sense of dryness in the nose and throat with difficulty in swallowing has also been observed with hypercalcemia (see p 301). Our patient, M. S. (M. G. H. 326829), was very interesting as regards these symptoms. It will be recalled that she was the married woman of 46 who had developed the swelling in the neck 14 years previous to admission, following

a miscarriage. Since the swelling subsequently proved to be a parathyroid tumor, one is justified in estimating the duration of her illness as fourteen years. At the time of the development of the swelling she noticed loss of strength, loss of appetite, loss of twenty pounds and constipation. These four symptoms were promptly relieved by operation and the restoration of the isoparathyroid state. Thus two months after the operation she was able to do her housework, whereas previously she had been unable to do any



Fig. 30 Patient with Hyperparathyroidism and Marked Hypotonicity. Note also tumefaction of left maxilla. [From Barr and Bulger (1930) with permission from the American Journal of the Medical Sciences.]

work. Her appetite became excellent, she gained 14 pounds and her bowels ceased to require daily cathartics. This same story can be duplicated in case after case.

The hypercalcemia undoubtedly affects other nervous mechanisms. Hunter and Turnbull (1931) observed increase in auditory acuity following removal of a parathyroid tumor. Furthermore patients not infrequently have transient trouble focusing their eyes after the hyperparathyroid state has been replaced by the isoparathyroid state.

Walsh and Howard (1947) have called attention to calcium deposits in the eyes in patients with hypercalcemia, whether due to vitamin D poisoning hyperparathyroidism or other causes such as sarcoid or the syndrome associated with excessive milk and alkali intake (see page 98). To see the crystals a slit lamp must be used. The deposits occur in the deep conjunctiva of the palpebral fissure; they may regress when the hypercalcemia is corrected. Cogan (1947) was able to confirm this finding at the Massachusetts General Hospital.

Another lesion 'band keratitis', was found by Cogan (1947) also to be associated with hypercalcemia. This same lesion was present in several of the cases studied by Walsh and Howard (1947). The deposits are in the superficial layers of the periphery of the cornea and are most marked at the palpebral fissures. In the later stages they can be seen by the naked eye.

(4) Hyperparathyroidism and Hematopoietic Function

In hyperparathyroidism with bone disease where there is marked fibrosis of the bone marrow one would expect an anemia and a leucopenia. Such is the case. Dr. Charles H. DuToit made a survey of the Massachusetts General Hospital cases and concluded that anemia was also frequent in the presence of complicating renal disease. He also found cases with marked bone disease without anemia. The anemia may respond to iron (see Case No. 1).

(a) Primary Hyperparathyroidism Without Bone Disease

As discussed under Pathologic Physiology (see page 23) there is a difference of opinion as to the cause of the bone disease in hyperparathyroidism. It is a fact however that one may have severe hyperparathyroidism and show no clinical, roentgenological or histological evidence of bone disease [Albright, Sulkowitch and Bloomberg (1937)]. Those who believe that the hormone acts directly on bone tissue would probably argue that such cases either are of short duration or that some evidence of bone disease would have been found had one biopsied the right bone tissue (e.g. trabeculae on the inside of the bone shaft rather than the cortex). This is not the authors' interpretation. In their opinion hyperparathyroidism brings about a change in the blood chemistry of the body which results in there being an increased excretion of calcium in the urine. Other things being equal this increases the chances of the patient being in negative calcium balance. If the patient is in negative calcium balance bone disease develops; if the patient happens to ingest sufficient calcium to compensate for the loss in the urine and feces the calcium balance is not negative and bone disease does not develop (see Fig. 11, p. 25). For all practical purposes, it usually comes down to whether or not the patient drinks milk.

If he does the calcium intake will be sufficient to keep a positive calcium balance even if he has marked hyperparathyroidism

It might be argued that hyperparathyroidism causes bone destruction and that those patients on a high calcium intake are able to balance this

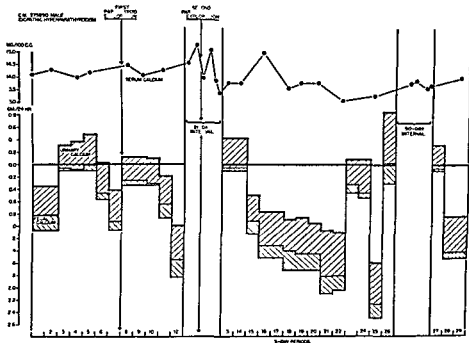
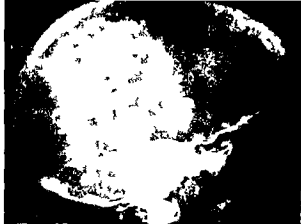


Fig 31 Metabolic Data on C M (M G H 275890) to Show Effect of Calcium Intake on Calcium Balances in Hyperparathyroidism

For construction of chart see Appendix p 309 Note that serum calcium is very high *circa* 14 mg, during entire experiment and is not influenced by negative parathyroid explorations Note that the calcium excretion in the urine is very high and by and large does not fluctuate materially with changes in calcium intake When calcium intake is high patient is in a strongly positive calcium balance when calcium intake is low, patient is in a negative calcium balance Note in the sixth metabolic period that the calcium intake was between 0.5 and 0.66 gm/day and the calcium output was approximately the same therefore 0.6 to 1.0 gm of calcium per day in the intake (i.e. about one quart of milk) would have kept this patient in positive calcium balance [From Albright (1947a), data recharted from Bauer, Albright and Aub (1930)]

destruction with new bone formation This is not the case because, if it were, one would see evidence of bone destruction and bone formation in bone biopsies Furthermore the phosphatase level, which is an index of bone formation (see p 6), would be increased, which it is not The phosphatase level, therefore, is an index not of the degree of hyperparathyroidism but merely of the degree of bone disease

(A)



(B)



(C)



Fig. 32 X-Ray Films of Skull Showing Increase of Bone Density in Hyperparathyroidism as a Result of High Calcium Diet

Latent N.B. (M.G.H. 70171) (A) July 28, 1930 (B) October 4, 1930 and (C) September 30, 1931 [From Albright, Baird, Cope and Bloomberg (1934)]

Fig 31 is very apropos of present discussion. It shows calcium metabolic data on Captain Charles Martell. It will be noted that by and large the calcium excretion in the urine remained fairly constant in spite of the marked fluctuations in the calcium intake and that he was in a positive calcium balance when his calcium intake was above 0.6 to 1.0 gm. of calcium per day. When one remembers that a quart of milk contains about one gram of calcium, it will be seen that a patient with a very marked degree of hyperparathyroidism such as he had can readily be kept in calcium balance. A further argument in favor of the authors' point of view is the fact that the bone disease in hyperparathyroidism can be made to regress with diet alone while the underlying degree of hyperparathyroidism remains the same (see Fig 32).

The following case illustrates the points just discussed.

Case No 2 Hyperparathyroidism due to Idiopathic Hypertrophy of All Four Parathyroid Glands With Nephrolithiasis but Without Bone Disease

W. P. (M. G. H. 340457) a single Finnish chauffeur of 39 entered the hospital October 4, 1934 because of attacks of right side pain. Retrograde pyelogram showed a right ureteral stone. He had lost 45 pounds by diet and exercise in the past two years. Physical examination was essentially normal. The stone was removed on October 6, 1934.

As with all patients who have a kidney stone serum calcium and ionized calcium determinations were done and found to be 11.3 and 2.3 mg. per 100 cc. respectively. These figures were checked at 12.2 and 2.6 mg. per 100 cc. and again at 13.0 and 2.0 mg. per 100 cc. and left no doubt that this patient had hyperparathyroidism of a fairly marked degree. Roentgenograms failed to show increased radiability of the skeleton and the serum phosphatase level was normal (3.7 to 3.0 Bodansky units).

On October 27, 1934, Dr. Oliver Cope performed a subtotal parathyroidectomy, tibial biopsy being taken at the same time. The parathyroids were all enormous, 4 gm. of tissue being removed. Fig 33 shows the parathyroid tissue removed. Fig 34A and 34B show low and high power photomicrographs of the tibial biopsy on this patient. It will be noted that the cortex was very thick and showed no rarefaction. Most important of all however was the fact that by high power there were no osteoclasts and no fibrosis—just fat cells and inactivity (compare Fig 34B with Fig 51A, p. 110).

This patient made an uneventful recovery and has remained well ever since.

(6) Clinical Types of Primary Hyperparathyroidism

From the previous discussion it is obvious that one can divide cases of hyperparathyroidism into the following groups:

- (A) With bone disease and without kidney disease
- (B) With bone disease and with kidney disease
- (C) Without bone disease and with kidney disease
- (D) Without bone disease and without kidney disease

Of the first 64 proved cases of the Massachusetts General Hospital series there were in group (A) 11 cases, in group (B) 24 cases, in group (C) 28 cases, and in group (D) 1 case. These figures suggest that kidney disease is more common than bone disease. It has been the experience of the authors and their colleagues that about five per cent of all patients with kidney stones in Boston have an underlying hyperparathyroidism as its cause.

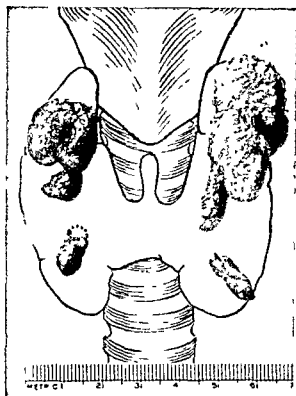


Fig. 33 Photograph of Parathyroid Tissue Removed at Operation on Patient 340157 with Hyperparathyroidism due to Parathyroid Hypertrophy

Area inclosed by dotted line at upper pole of lower right parathyroid gland represents amount of gland tissue left *in situ*. Centimeter rule at bottom indicates enormous size of glands. [From Albright, Sulkowitch, and Bloomberg (1937)]

One further word might, perhaps, be said about group (D). If one can have hyperparathyroidism without bone disease and with kidney disease or without kidney disease and with bone disease, it is apparent that cases will occur *without bone disease and without kidney disease*. These cases may very well be miserable because of the symptoms due to hypercalcemia *per se* (*vide supra*). The authors have seen one such case up to 1917 in a series

of 83 proved cases. The credit for diagnosing this case goes to Dr S H Iu of Peiping, China, who sent the patient to Boston for operation.

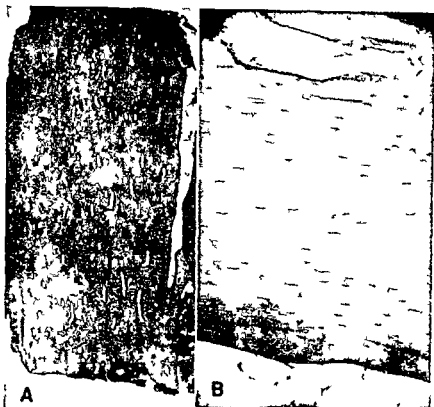


Fig. 34 Photomicrographs from Bone Biopsy to Demonstrate Absence of Histological Evidence of Bone Disease in Case of Marked Hyperparathyroidism.

A—low power B—high power. Note complete absence of resorption (A) and of osteoblastic and osteoclastic activity (B). Compare with similar changes in osteoporosis (see Fig. 51A). (Patient MCH 3401a.) [From Allright, Sulzowitch, and Bloomberg (1937).]

(E) *Diagnosis of Primary Hyperparathyroidism*

Once the diagnosis of hyperparathyroidism has been suspected because of the finding of a calcium stone or certain bone changes, or because of certain symptoms suggesting hypercalcemia, its confirmation in most instances depends on the finding of a high serum calcium level coupled with a low serum phosphorus level. If the patient has a marked degree of the disease, these values will be sufficiently abnormal so that other diagnostic procedures are superfluous. To be sure, there are other causes for hypercalcemia which will be discussed under Differential Diagnosis of Primary Hyperparathy-

roidism' (see p 81) But these seldom offer difficulties as it is most unusual to have the hypercalcemia coupled with hypophosphatemia. In very rare instances of multiple myeloma or metastatic malignancy, however, one will find hypercalcemia with hypophosphatemia, but there one will find other differential points (*vide infra*)

It should be emphasized again that the serum phosphatase level is not a test which should be used in determining whether or not a patient has hyperparathyroidism since its level is perfectly normal if the hyperparathyroidism is not associated with bone disease. The test should only be used in determining the degree of bone disease once the diagnosis has been established. To be sure, if one has a patient with marked bone disease as shown by x-ray and the serum phosphatase level is not elevated, one is pretty safe in ruling out hyperparathyroidism as a cause of the bone disease.

The Sulkowitch reagent (see page 302) is very useful as a rough bedside test to determine whether hypercalcemia is present or not. For example, if a patient has a kidney stone of unknown etiology, it is of interest to perform this test. If there is very little calcium in the urine, hyperparathyroidism is very unlikely and one will probably be content with one normal serum calcium and phosphorus determination in ruling the condition out. However, if the urine tests show large amounts of calcium repeatedly, then one has to be very cautious about ruling out hyperparathyroidism even if the first calcium and phosphorus levels are within normal limits (*vide infra*).

It is obvious from the nature of hyperparathyroidism that there will be cases ranging from a marked degree of the disease all the way down to the normal state. The less the degree of hyperparathyroidism, the less the chemical findings will deviate from the normal and the more difficult the diagnosis will be. One is often asked how high the serum calcium level must be before one considers hyperparathyroidism. This of course is impossible to state. In some instances one considers the diagnosis even with a normal serum calcium value. It must be remembered that if one gives parathyroid extract to a normal individual, one can double the calcium excretion in the urine without appreciably altering the blood values. In Fig. 35 the average pre-operative serum calcium values on the first thirty-five patients of the Massachusetts General Hospital series with hyperparathyroidism proved by operation are plotted in order of increasing calcium values. It will be seen that nine patients had average serum calcium values below 12 mg. and one patient had an average serum calcium value below 11 mg.

In this group of patients where small elevations in the serum calcium level are significant, the serum protein determination becomes of the utmost importance (see discussion above under 'State of Calcium in Serum', p. 7). It will be remembered that the amount of ionized calcium depends on the

degree of hyperparathyroidism, while the amount of calcium bound to protein is a function of the amount of protein as well as of the amount of ionized calcium. It is apparent, therefore, that the ionized calcium may be slightly high due to a mild degree of hyperparathyroidism and yet, if at the same time the patient has a low serum protein level the calcium bound to protein will be low so that the net result may be that the total calcium is normal. It, therefore, becomes necessary in instances where the serum

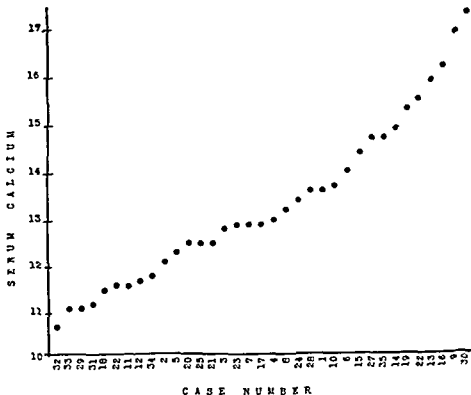


Fig. 35 Average Pre-operative Serum Calcium Values on First 35 Patients with Hyperparathyroidism of Massachusetts General Hospital Series [From Albright, Sulkowitch and Bloomberg (1937)]

protein is low to make an allowance in the total serum calcium value for what the value would have been had the serum protein been normal. This can easily be done from the linear chart published by McLean and Hastings (1935) (see Fig. 3, p. 8).

Since the calcium excretion in a patient on a low calcium diet may increase 100 per cent on the administration of parathyroid extract without an appreciable change in the serum calcium level, it is obvious that in the diagnosis of cases with a very mild degree of hyperparathyroidism it will be

useful to make accurate determinations of the urinary calcium excretion under standard conditions. Furthermore, a low serum protein level will not influence the urinary calcium excretion since the latter depends on the ionized rather than on the total calcium level of the serum.* In order to obtain urinary calcium-excretion data, it is of course, necessary that one follow some standard procedure. The authors have their patients take a neutral ash low calcium diet† for one week and collect a 24 hour urine specimen. One would obtain, of course, higher urinary calcium excretions with bedridden patients (see discussion under 'Osteoporosis from Disuse', p 147). Although the authors have not very many data from normal individuals on this regimen, they consider a urinary calcium excretion of 150 mg per day as suggestively high, and one of 200 mg or more per day as distinctly high. Of course, whether the information obtained in this way will establish the diagnosis will depend on the clinical picture as a whole. As in most other diseases no one laboratory finding absolutely makes the diagnosis.

* It must be stated, however, that the urinary calcium excretion is low in nephrosis [Emerson and Beckman (1915)]

† The diet used by the authors is as follows

<i>Breakfast</i>	Orange juice—1 small glass Cooked farina or rice— $\frac{1}{2}$ cup after cooking 4 Uneda biscuits Oleomargarine 3 strips of crisp bacon Coffee or tea Salt and sugar
<i>Noon</i>	Lean meat—medium sized serving Potatoes—1 medium sized White corn— $\frac{1}{2}$ cup 4 Uneda biscuits Oleomargarine Applesauce— $\frac{1}{2}$ cup—or 1 medium sized apple Tea salt and pepper sugar
<i>Light</i>	Chicken—1 medium serving Macaroni— $\frac{1}{2}$ cup (cooked) Canned tomato— $\frac{1}{2}$ cup 4 Uneda biscuits Oleomargarine Banana—1 medium sized Tea or coffee Salt, pepper sugar
<i>Note</i>	Use oleomargarine and sugar generously to keep up weight. Absolutely no butter, milk, cheese or cream. This diet contains approximately 0.137 grams of calcium. Caution must be exercised to avoid cereals and oleomargarine which have been fortified with additional calcium.

The following case abstract emphasizes some of the points which have been discussed in regard to the diagnosis of hyperparathyroidism in patients with a minimal degree of the disease

Case No 3 Hyperparathyroidism of Mild Degree Without Bone Disease but With Nephrolithiasis

E B , (M G II 36569) a married woman of 48 came to the clinic on February 21, 1936 because of bilateral kidney stones Her first symptoms of nephrolithiasis had developed in 1932 and a stone had been removed from the right kidney in



Fig 36 Photomicrograph of Parathyroid Tumor in Case No 3

Note that a large pedicle of normal parathyroid tissue is still intact (on the left) Note colloid in tumor, which might suggest thyroid tissue to an inexperienced pathologist Tumor measured 1.1 by 0.6 by 0.3 cm (From Albright, Sulkowitch, and Bloomberg (1937))

1933 She had taken large amounts of milk so it was not surprising that there were no bone symptoms Physical examination was non contributory Roentgenograms showed multiple, bilateral renal calculi and normal appearing bone Urine showed large amounts of calcium, no albumin, no bacteria (sterile cultures), a few red cells, but no white cells The stones in the right kidney, which were causing considerable pain, were removed on March 4 1936 The serum calcium values, with possibly two exceptions, were within normal limits, the serum inorganic phosphorus level was persistently low (circa 2.5 mg per 100 cc), the serum phosphatase level was normal (cf no bone disease)

The presence of a normal serum calcium with a low serum phosphorus, of course, suggested hyperparathyroidism with a low serum protein, the latter determination was accordingly done and found to be 5.0 gm per cent It was found

that if one corrected the serum calcium value to what they would have been had the serum protein level been normal one obtained instead of 10.3 and 10.8 mg., 11.0 and 12.0 mg. per 100 cc. The corrected values were highly suggestive of hyperparathyroidism. In addition the patient excreted 263 and 222 mg. of calcium per 24 hour period while on the low calcium diet. Furthermore the stones were found to consist largely of calcium phosphate and no other cause for stones was found—no obstruction—no infection. A diagnosis of mild hyperparathyroidism was accordingly made.

On March 23, 1936 Dr. Edward D. Churchill removed a small adenoma in the left lower parathyroid (1.1 by 0.6 by 0.3 cm.) (see Fig. 36). Following the operation the serum phosphorus level rose to 4.2 and 3.6 mg. per 100 cc. and the patient had no further stone formation.

This case is an excellent example of the importance of the serum protein determination, it illustrates furthermore, the value of urinary calcium determinations as confirmatory evidence.

(F) Parathyroid Poisoning

By "parathyroid poisoning" is meant a sort of hyperhyperparathyroidism. If one administers parathyroid extract in large quantities to dogs death will occur in two or three days preceded by anuria and retention of nitrogenous products [Collip (1926)] and at autopsy there will be calcium deposits in many tissues notably the alveoli of the lungs, the mucous membranes of the stomach, the thyroid, and the kidneys [Hueper (1927)] (see Fig. 37). The sequence of events leading up to death may be as follows: an increasing high serum calcium value, inspissation of the blood dependent on the hypercalcemia, a resulting acute failure of kidney filtration rapidly rising serum phosphorus and non protein nitrogen levels, the combination at the same time of a high serum calcium and a high serum phosphorus level, precipitation of calcium phosphate into the tissues, and chemical death.

Grollman (1927) in fact has shown that at high levels of serum calcium (circa 18.0 mg.) phosphate is no longer 100 per cent filterable. Precipitation is especially apt to occur wherever there is a localized alkalosis. This one would expect in any organ which is exerting acid, thus is explained the precipitation of calcium phosphate in the lungs, the stomach, and the kidneys which excrete carbonic acid, hydrochloric acid, and phosphoric and various organic acids, respectively. Why calcium should also be deposited in the thyroid is far from clear. The end result, which Virchow designated "calcium metastases", is not confined to parathyroid poisoning but is met in any condition where the serum contains excessive amounts of calcium and phosphorus notably chronic renal insufficiency with phosphate retention, vitamin D poisoning (see p. 9), and metastatic disease of the bones.

Patients with hyperparathyroidism seldom have such a degree of the disease that there is much danger of their developing parathyroid poisoning.

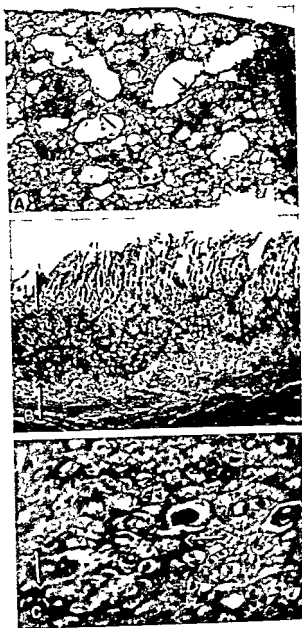


Fig 37 Photomicrographs of Tissues from Dog Which Died of Parathyroid Poisoning

A—lung, B—mucosa of stomach, C—kidney. Tissues stained with von Kossa's silver stain so that calcium is black. Note lacework of calcium around each alveolus in the lung, band of calcium around glands in stomach mucosa, and peri tubular deposit of calcium in kidney. [From Erdheim and Albright (unpublished data)]

About 17 mg per 100 cc is the critical level of serum calcium above which poisoning is to be feared. A case history reported by Dawson and Struthers (1923) is probably an example of acute parathyroid poisoning due to a parathyroid tumor. The patient a forty nine year old laborer who for several years had had symptoms referable to his skeleton was seized with a heart attack and taken to the hospital in a state of collapse. He was too ill to give an account of himself and died suddenly the following morning without any precise conclusion as to the cause of the collapse having been arrived at. Autopsy revealed osteitis fibrosa generalisata in an early stage a parathyroid adenoma one inch in length and calcium deposits in all the internal organs notably the internal elastic lamina of the arteries the heart wall the lungs stomach and kidneys. There seems no question but that this patient was suffering from parathyroid poisoning which caused a chemical death. Similar cases were reported more recently by Oliver (1939) Hanes (1939) and Smith and Cooke (1940).

The importance of parathyroid poisoning from a clinical point of view has to do with its prevention. If the serum calcium level in a patient is near the critical level a slight increase may precipitate parathyroid poisoning. It may so happen that the giving of a high calcium diet would make the difference. In the authors opinion a patient with severe hyperparathyroidism should be kept on a low calcium intake for this reason. One's first impulse if the patient has marked bone disease may be to order a high calcium diet this may be fatal. The authors rather believe that some of the patients with hyperparathyroidism in other clinics who have died under rather mysterious circumstances shortly after entering the hospital may have had parathyroid poisoning. No patient as yet of the Massachusetts General Hospital series has developed fatal parathyroid poisoning although one patient who was referred to the hospital from another clinic probably had the first stages of this condition brought on by a high milk intake. He entered the hospital with rising serum non protein nitrogen and phosphorus levels and a falling serum calcium level. A low calcium diet and intravenous saline medication were immediately started and the patient survived.

The danger signals which suggest the onset of parathyroid poisoning are rising serum phosphorus and non protein nitrogen levels and a sharp fall in the urinary volume. Hanes (1939) reported the case history of a woman of 19 years who had had a long history of urinary complaints and who had definite nephrocalcinosis. On the fourth day after admission her serum calcium was 20.0 mg and her serum phosphorus 4.7 mg per 100 cc. on the seventh day the corresponding values were 22.0 mg and 4.8 mg respectively and her plasma non protein nitrogen level was 58 mg per 100 cc. A parathyroid exploration was scheduled but was postponed because the

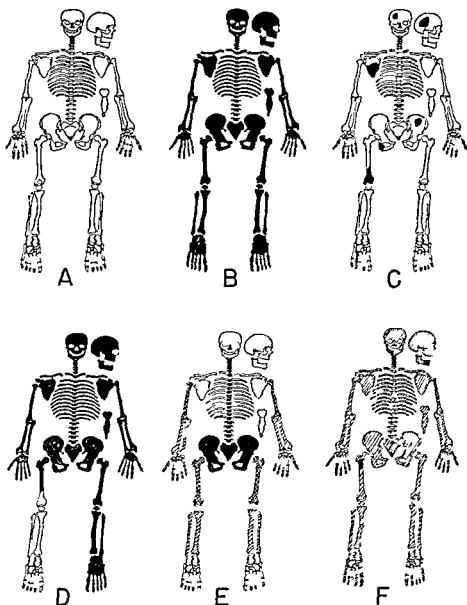


Fig 38 Diagrams to Illustrate Differences Between 'Generalized Bone Disease' and 'Localized Bone Disease' As Here Defined

In these diagrams a black area represents marked bone disease a shaded area mild bone disease. A and B represent no bone disease and generalized bone disease respectively and require no comment. C represents a form of localized bone disease albeit with disseminated lesions such as might be seen in polyostotic fibrous dysplasia. D depicts a condition where, though the lesions are widely spread there is a sharp line

patient rather suddenly developed marked weakness and a slight temperature. She died quite unexpectedly. Autopsy revealed besides a large parathyroid tumor, nephrocalcinosis, wide spread necrosis and calcification of the connective tissue, and calcium deposits in the stomach and lungs. Hanes attributes the changes in parathyroid poisoning to tissue necrosis rather than to a primary deposition of calcium, the authors are inclined to believe that necrosis is secondary to calcium deposition.

Shelling (1935) explains parathyroid poisoning in a somewhat different way from that discussed above. He emphasizes the diuresis caused by the parathyroid hormone and thinks that the acute kidney shut down associated with parathyroid poisoning is due to dehydration. For therapy he advocates intravenous saline.

(G) *Differential Diagnosis of Primary Hyperparathyroidism*

The discussion in this section will be confined to (a) other bone diseases which might be mistaken for hyperparathyroidism and (b) other causes for hypercalcemia.

A bone disease to be the result of hyperparathyroidism must be generalized. A metabolic disorder, by and large cannot produce a spotty disorder, it cannot affect all the bones of one limb and miss those of the other entirely, it should not stop at the midline. However, whereas the fundamental lesion—decalcification in the case of hyperparathyroidism—may be generalized it is perfectly possible for secondary lesions—cysts and tumors—to be localized. Under such circumstances the superficial observer may have his attention called to the *secondary lesions* and miss the less conspicuous but more fundamental underlying generalized lesion (see Fig 38). Furthermore, by 'generalized' the authors mean involving one hundred per cent of the skeleton. Thus, the lesions of Paget's disease the authors consider as localized (see p 284). Paget's disease may be very widespread and involve 95 per cent of the skeleton, the remaining 5 per cent, however, will be normal and there will be a sharp line of demarcation

of demarcation between abnormal and normal bone, the condition therefore not being a generalized bone disease is by definition a localized bone disease. The authors have Paget's disease in mind. *E* represents a generalized bone disease in spite of the fact that certain bones are not involved. It is considered generalized because there is a rhyme and a reason to the involvement, thus there is a predilection for the spine and pelvis while the skull and certain other bones escape. The authors have osteoporosis in mind. *F* represents a generalized bone disease although the casual observer might have his eye attracted by the areas of marked bone disease in the jaw at the upper end of the right femur and at the upper end of the left humerus and miss the generalized decalcification, the authors have *osteitis fibrosa generalisata* in mind here, where there is generalized decalcification often together with superimposed cysts and tumors.

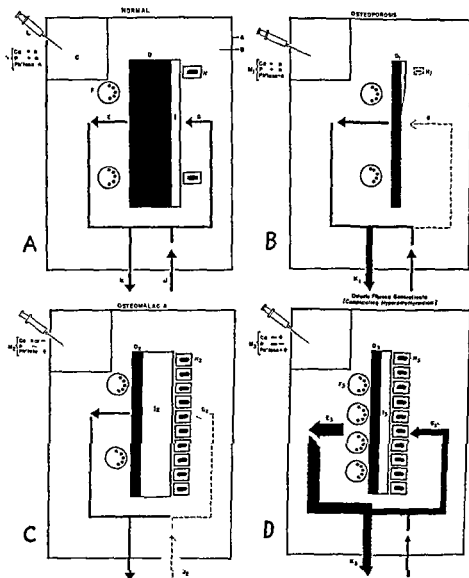


Fig 39 Schematic Diagrams to show Authors' Conception of Differences between Normal Bone (A), Osteoporosis (B), Osteomalacia (C) and Hyperparathyroidism With Bone Disease (D)

A—body limits, B—body fluid, C—body serum, a compartment of body fluid easy to tap for analysis, D—bone mass with two surfaces, one where bone is being resorbed and one where it is being laid down, E—arrow indicating by its size rate of Ca and P resorption, F—osteoclast, G—rate of Ca and P deposition, H—osteoblast laying down, I—osteoid, J—Ca and P entering body from gastro intestinal tract, K—Ca and P

between the normal and the abnormal. This is strong evidence against its being a metabolic disease. On the other hand, in senile osteoporosis (see p 162), which the authors consider a metabolic disease and hence generalized, large portions of skeleton may escape involvement (see Fig 38). However, there *one finds a rhyme and a reason which governs which are involved*. Thus, that condition has a predilection for the spine and pelvis, the extremities are involved to a less extent, the skull is almost never involved.

(1) Demineralization due to Metabolic Bone Disease

A Osteoporosis

This condition will be discussed extensively in Chapter 6 (see p 145). For its pathologic physiology in relation to other metabolic bone disease, see discussion under "Pathologic Physiology of Osteoporosis, Osteomalacia, and Osteitis Fibrosa Generalisata", p 141.

Osteoporosis has many causes, commonest of which are (1) post-menopausal state, (2) old age, and (3) Cushing's syndrome.

In osteoporosis the serum calcium and phosphorus values, with one important exception which will be discussed below (see p 84), are normal. Since there is considerable evidence that the serum phosphatase level in the absence of liver disease is an index to osteoblastic activity (see p 6) and since the fundamental disorder in osteoporosis is hypofunction of the

leaving body by kidney or other exits. L—syringe obtaining serum for analysis, M—blood values (n = normal, + = high, - = low).

Diagram A Note that calcium and phosphorus going into bone equals that coming out of bone, that part of that which comes out goes back in.

Diagram B Note decrease in bone mass (D_1) due to primary hypoplasia of osteoblasts (II_1) with resulting decreased deposition of osteoid (I_1) and decreased calcium and phosphorus deposition (G_1). Note also increased calcium and phosphorus excretion (K_1) because of less calcium being deposited in the bone, note also normal blood values (M_1).

Diagram C Note decreased bone mass (D_2) resulting from inability of calcium to be deposited in osteoid tissue (G) because of abnormal blood findings (M_2) with resulting wide osteoid seams (I_2) and an increased activity of osteoblasts (II). The condition is usually due to faulty calcium absorption (J_2).

Diagram D Note increased calcium and phosphorus excretion in urine (K_2) leading to increased bone resorption (F_2) with an increased number of osteoclasts (F_2) and resulting in decreased bone mass (D_2), which in turn necessitates increased bone formation with increased number of osteoblasts (II_2). In spite of the fact that serum phosphorus is low (M_2), serum calcium is sufficiently high (M_2) so that calcium can be deposited in newly formed osteoid (I_2) and calcium deposition is therefore increased (G_2).

[From Albright, Smith, and Richardson (1941), Reifenstein and Albright (1941), and Albright (1947a)]

osteoblasts, one would expect normal or low phosphatase levels in this disease. Such is the case. The calcium excretion in the urine may be markedly increased in the early stages when it may give rise to kidney complications, in the later stages of the disease it is normal or decreased. The reason for the increased calcium excretion in the early stages is probably the following. Normally some of the calcium and phosphorus which is set free by the process of bone resorption is used again for bone formation. It follows that any curtailment of this latter process will increase the calcium and phosphorus excretion in the urine (see Fig 39). However once the skeleton has become very depleted the calcium and phosphorus derived from bone resorption will be very small even though the amount of resorption taking place per unit of skeleton remains constant. When this situation has arisen, the urinary calcium and phosphorus excretion will be normal or even low. Hence, the hypercalcaemia and the hyperphosphaturia disappear after the skeleton becomes demineralized in osteoporosis in contradistinction to hyperparathyroidism, where they persist regardless of the degree of decalcification.

As suggested in Fig 38 the distribution of the lesions in metabolic forms of osteoporosis is quite distinguishing. It should be remembered that the skull is almost never involved whereas it is one of the first parts to become affected in hyperparathyroidism almost the only exception to this rule in the authors' experience occurs in severe cases of Cushing's syndrome. It is often easier to get satisfactory x-rays of the skull than to have the necessary extremely accurate blood chemical determination carried out. The lamina dura likewise is seldom absent in osteoporosis. Furthermore in osteoporosis one does not find cysts and tumors merely demineralization and deformities or fractures.

1 Osteoporosis Associated with Hypercalcaemia in Childhood It was stated above that there is one important exception to the assertion that the serum calcium and phosphorus values are normal in osteoporosis. This exception occurs when a large proportion of an actively changing child's skeleton is suddenly put into forced disuse. Apparently the calcium coming from the immobilized parts because of disuse atrophy (see p 117) is so great that the kidneys cannot clear the serum of excess calcium and hypercalcaemia results. The serum phosphorus in such cases as one would expect is normal or slightly elevated the serum phosphatase as in other instances of osteoporosis is normal. One meets the situation shortly after the onset of infantile paralysis or after a child has been put into a plaster cast. An analogous situation occurs in adults when a person with excessive bone formation compensatory to increased bone destruction as with Paget's disease is suddenly immobilized (see discussion on p 200). The following

case illustrates this exception in an actively growing child [Albright, Burnett, Cope, and Parson (1941)]

Case No. 4 Pathological Fracture Through Localized Osteitis Fibrosa of Right Femur, Hypercalcemia from Acute Osteoporosis of Disuse

A. T. (M. G. H. 260916) a 14 year old school boy was perfectly well and active until two months before admission when he jumped on home plate after making a home run and fractured the neck of the right femur. X rays demonstrated a



Fig. 40 Case No. 4 Acute Osteoporosis of Disuse Pathological Fracture through Localized Osteitis Fibrosa of Right Femur

[From Albright, Burnett, Cope, and Parson (1941)]

cyst at the site of fracture (Fig. 10) but normal bones elsewhere. He underwent an open reduction and then was put into a spica cast which immobilized him from the waist down. The patient did not do well but suffered from anorexia and had episodes of vomiting. He developed hematuria on one occasion, but no gravel was demonstrated. The surgeon in charge, Dr. Alexander P. Aitken, found a

marked hypercalcemia and very logically, concluded that the patient had an underlying hyperparathyroidism with gastric symptoms due to hypercalcemia *per se*

On admission the patient had a high serum calcium 14.6 mg per 100 cc, a normal serum phosphorus for a growing boy, 4.5 mg per 100 cc, and a normal serum phosphatase for a growing boy, 60 Bodansky units. There was extreme demineralization of the immobilized parts of his skeleton but the remainder of his skeleton was normal (Fig. 41), the lamina dura was easily visible (Fig. 42). The urine contained huge amounts of calcium and the sediment showed many calcium phosphate casts.

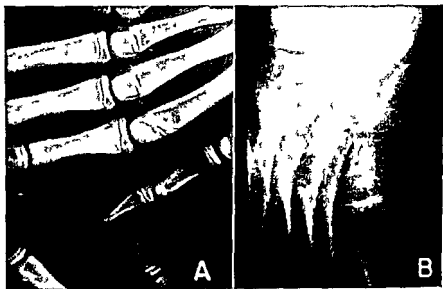


Fig. 41 Case No. 4 Acute Osteoporosis of Disuse. X-ray Films Contrasting Normal Density of Parts of Skeleton Not Immobilized [Hand (A)] with Decreased Density of Parts of Skeleton Immobilized [Foot (B)]
[From Albright, Burnett, Cope and Parson (1941)]

A diagnosis of hyperparathyroidism was made. The absence of hypophosphatemia was a little disturbing but was explained on the basis of beginning renal insufficiency. It was thought that he had no bone disease due to hyperparathyroidism and that the cyst in his right femur was a 'solitary cyst' and an unrelated finding. The neck was explored at one operation and the anterior mediastinum at another without the finding of a parathyroid tumor. It was not until then that it was realized that the sequence of events probably was (A) 'solitary cyst', (B) fracture through 'cyst', (C) immobilization (D) osteoporosis of disuse and (E) hypercalcemia due to very rapidly developing osteoporosis. It was accordingly decided, since the patient was rapidly going downhill that activity must be started. Therefore he was allowed to bear weight on the fractured leg. In one month's time the serum calcium fell from 14.4 to 11.3 mg per 100 cc, the serum phosphorus fell from 4.4 to 3.6 mg per 100 cc, and the serum phosphatase rose from 5.8 to 8.3 Bodansky units (Fig. 43). With reduction

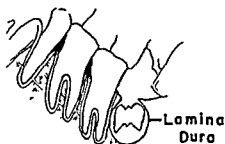


Fig 42 Case No 4, Acute Osteoporosis of Disease X ray Films Showing Presence of Normal Lamina Dura

[From Albright, Burnett, Cope, and Parson (1941)]

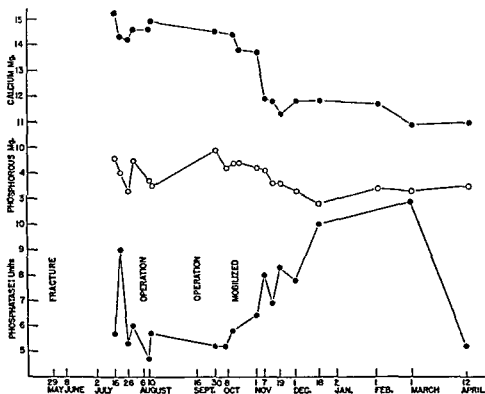


Fig 43 Case No 4, Acute Osteoporosis of Disease Chart Showing Relation of Serum Calcium, Phosphorus and Alkaline Phosphatase to Time of Fracture Parathyroid Operation, and Mobilization

Note that with mobilization there was a fall in serum calcium and phosphorus values and a rise in serum alkaline phosphatase values [From Albright, Burnett, Cope, and Parson (1941)]

in the hypercalcemia the anorexia and vomiting disappeared and the patient made an uneventful recovery.

In summary, therefore, osteoporosis is the bone disease which most often has to be differentiated from hyperparathyroidism. It occurs as a result of disuse, in senility, in women after the menopause, and in Cushing's syndrome. It has a predilection for the pelvis and spine and seldom involves the skull or lamina dura. It is the only metabolic bone disease which has a normal serum phosphatase level in the presence of markedly diminished bone density. The serum calcium and phosphorus levels are usually normal except in growing children when, following immobilization of large parts of the skeleton there may be hypercalcemia without hypophosphatemia. Hypercalcemia is present only in the early stages of the disease, when it may be very marked.

B *Osteomalacia and Rickets*

The pathological physiology of osteomalacia and its differentiation from osteitis fibrosa generalisata is shown in Fig 39, p 82. The subject as a whole and its etiology will be discussed at length in Chapter 7 (see p 205).

The serum findings serve to differentiate osteomalacia from hyperparathyroidism with osteitis fibrosa generalisata. Where both conditions usually have low serum phosphorus and high serum alkaline phosphatase levels, the serum calcium level is characteristically normal or low in osteomalacia and high in hyperparathyroidism. Furthermore, urinary calcium excretion is reduced in certain forms of osteomalacia, whereas it is almost always high in hyperparathyroidism.

Both conditions present generalized decalcification and absent lamina dura. Tumors and "cysts" are rarely, if ever, found in osteomalacia and deformities occur as a result of bending rather than fractures. An exception to this statement is the presence of "pseudo-fractures" described by Milkman (see p 206).

What has been said for osteomalacia holds equally well for rickets. In this latter condition one has the additional differential point that hyperparathyroidism does not cause wide and irregular epiphyseal lines.

C *Osteogenesis Imperfecta*

Although there is considerable confusion about terminology, no distinction is here made between osteogenesis imperfecta fragilis osium, and osteoporosis. The malady is not to be confused with Albers-Schonberg's disease or marble bone, which is also an hereditary disease associated with bone fragility.

Osteogenesis imperfecta is an hereditary disease and probably involves

all mesenchymal tissue, indeed Key (1926) has termed the condition 'hereditary hypoplasia of the mesenchyma' The disturbance in the bone is closely akin to that met with in osteoporosis However, instead of there being an hypoplasia of the osteoblasts, there is apparently a failure of the osteoblasts to form the normal amount of extra-cellular substance The end result, it will be seen, would be very much the same, that is, too little bone matrix However, the osteoblasts are actually increased in numbers and the osteocytes in the bone which is formed are of course, closer together It is not so surprising, therefore, that in many but not all cases there is a moderate increase in the serum phosphatase level [Smith and Mitchell (1935)] Patients with this disease are very subject to fracture not only because the bones are thin but also because the bone itself is brittle In fact, in contradistinction to osteitis fibrosa generalisata, the fractures tend to occur where the bone is thickest

Besides the bone pathology in osteogenesis imperfecta one meets disturbances in the other tissues of mesenchymal origin Thus, the sclerae almost invariably appear blue because, due to their thinness, the choroid shows through, furthermore, the blood vessels, fascia, periosteum, and subcutaneous tissues are all very pliable The condition is apparently a dominant characteristic and is passed on from one generation to the next The bone disease varies in severity from a condition incompatible with life to one which causes only moderate disability, it improves when adult life is attained, at which time otosclerosis is apt to develop

From the above discussion it is clear that only a rare case without a history of multiple fractures from birth on is apt to be confused with osteitis fibrosa generalisata For example, the bone disturbance might be first recognized at the age of fifteen when x rays, which perhaps were taken because of a fracture, revealed a generalized thinness of the skeleton The x ray of the skull, which will show a very thin, but not a decalcified skull is at once enough to rule out the bone disease of hyperparathyroidism (see Fig 27D) Furthermore, the lamina dura will be intact The sclerae will be blue The serum calcium and phosphorus will be normal There will be no hypercalcaemia or hyperphosphataemia The serum phosphatase, to be sure, may be slightly elevated There probably will be a family history of fractures blue sclerae, or otosclerosis The differential diagnosis should present no difficulty

(2) Demineralization due to Localized Bone Disease

There will now be considered a few of the localized bone diseases which may be mistaken for hyperparathyroidism The authors' concept of 'localized' has been stated above By definition this group of diseases can be differentiated from osteitis fibrosa generalisata by the demonstration

of absence of decalcification somewhere in the skeleton. The lamina dura, for example, should be demonstrable around the teeth if the jaws do not happen to be involved in the localized process.

A *Polyostotic Fibrous Dysplasia (Osteitis Fibrosa Disseminata)*

This curious syndrome will be discussed in more detail in Chapter 8 (see p 263). It is constantly being mistaken for hyperparathyroidism although the diagnosis if one keeps to first principles should offer no difficulty. The authors have had an opportunity to study many of these cases which have been operated upon for hyperparathyroidism in other clinics with negative parathyroid findings and sent on to the Massachusetts General Hospital for further study.

Briefly state the characteristics of the syndrome are (a) a disseminated osteitis fibrosa (both hyper- and hypo-ostotic) with a segmental distribution suggesting a neurologic or embryologic relationship (b) areas of cutaneous and, in one instance buccal pigmentation which have a distribution suggesting some connection between them and the bone lesions and (c) sexual and somatic precocity in females but not in males.

The first differential point between this syndrome and the osteitis fibrosa generalisata of hyperparathyroidism is the fact that the bone lesions in the former condition albeit widely disseminated in certain cases are not generalized the uninvolved parts of the skeleton are completely normal. This distinction immediately rules out a hormonal or metabolic disorder, hormones do not affect one leg and not the other, hormones do not stop at the midline. The second point in differential diagnosis is the fact that the bone lesions are hyperostotic as well as hypoostotic, in hyperparathyroidism hyperostosis is most unusual. Thus, whereas the typical appearance of the skull in osteitis fibrosa generalisata is one of generalized demineralization the typical appearance of the skull in the syndrome under discussion is a marked increased density at the base of the skull coupled with a localized (often confined to the occiput) increased thickening of the vault of the skull somewhat reminiscent of that seen in Paget's disease (compare Fig 137A p 271 with Fig 27E, p 61). The third point in differential diagnosis is the blood chemistry. The serum calcium and phosphorus levels are normal in polyostotic fibrous dysplasia as compared with the high serum calcium and low serum phosphorus levels in hyperparathyroidism, both conditions can have a high serum phosphatase level. The precocity in females and areas of cutaneous pigmentation, though striking when present, are not sufficiently constant to constitute important differential points.

B *Paget's Disease (Osteitis Deformans)*

This condition will be discussed extensively in Chapter 9 (see p 284). There should be no difficulty in distinguishing it from hyperparathyroidism with osteitis fibrosa generalisata. The serum calcium and phosphorus values are normal while the serum alkaline phosphatase is elevated more per unit of bone disease than it is in osteitis fibrosa. When the disease is advancing there may be hypercalcaemia and even nephrolithiasis but renal complications are less common than in hyperparathyroidism. The skeletal involvement is 'localized' (i.e., not generalized) and there is a tendency to overgrowth of involved bones.

C *Osteitis Fibrosa Localisata (Solitary Bone Cyst)*

Solitary lesions which on biopsy are indistinguishable from osteitis fibrosa generalisata and osteitis fibrosa disseminata are apt to occur at the ends of the long bones, notably the upper end of the femur where they not infrequently lead to pathological fractures (see Fig 40 and Case No 4, p. 85). Thus, one finds [Mandl (1926)] the brown tumor, the smooth walled cyst lined with fibrous tissue, the fibrous replacement of bone marrow, *et cetera*. All these lesions masquerade under the x-ray diagnosis of a "cyst". By 'cyst' is meant almost any circumscribed lesion showing absence of calcified bone.

D *Multiple Myeloma*

Multiple myeloma can produce a clinical picture which may be most difficult to distinguish from hyperparathyroidism. The x-ray appearance of the bones can be quite similar although in most instances the lesions in multiple myeloma are more sharply demarcated. For example, one expects punched out areas in the skull rather than a diffuse 'moth-eaten skull' (see Fig 27F, p 61). The serum calcium can be high in myeloma when it is the calcium excretion in the urine is also high and nephrolithiasis may be present. The high serum calcium level is usually coupled with a normal or high serum phosphorus level. In some cases, however, the serum phosphorus level is low just as it is in hyperparathyroidism. The presence of large amounts of Bence-Jones protein in the urine is strong evidence for myeloma, their absence means very little as in thirty cases of proved myeloma studied by Jacobson and Milner (1944) it was found in only fifteen cases. Whether small amounts of this protein may be present with the bone disease in hyperparathyroidism is still questionable since, in those cases where it has supposedly been found, the most rigid criteria probably were not applied. Of course, the presence of plasma cells in the peripheral

blood or hyperglobulinemia are strongly suggestive of myeloma and a positive finding in a sternal biopsy or puncture is pathognomonic for myeloma. The serum phosphatase is rarely, if ever, elevated in myeloma, an important differential point [Bodansky and Jaffe (1934), Gutman, Tyson and Gutman (1936), and Jacobson (unpublished data)]



Fig. 44 X-ray Film Showing Metastasis of an Hypernephroma to Skull

Note sharply demarcated areas of bone destruction (cf. Case No. 5 p. 93 ALG II 57634)

L. Metastatic Malignancy

Metastatic malignancy offers little difficulty in the differential diagnosis. The x-ray appearance is quite distinguishing (see Fig. 44), the individual lesions are as a rule sharply demarcated and areas of normal bone can almost invariably be found. The serum calcium may be high and there may be hypercalcaemia and kidney stone formation. The serum phosphorus is usually normal occasionally elevated and only very occasionally decreased. The phosphatase level may be elevated. A primary source is to be looked for and is most apt to be found in the breasts prostate kidneys (hypernephroma), bronchus, or thyroid.

Cases of multiple myeloma and metastatic malignancy with hypercalcemia are most interesting from an academic point of view. The question arises as to what is the cause of the hypercalcemia. The most obvious and probably the correct explanation is that the metastatic lesions are dissolving bone salts into the blood stream more rapidly than the kidney can clear the blood of excess calcium.

Those cases, which are very much in the majority, in which the hypercalcemia is not associated with a hypophosphatemia are an argument in favor of the authors' thesis that the parathyroid hormone acts on the blood chemistry rather than on bone tissue. If the action of the hormone were on the bone, one should get the same blood findings as one obtains in metastatic malignancy. For the same reason those rare instances of metastatic malignancy in which the hypercalcemia is associated with hypophosphatemia are an argument against the authors' point of view.

From an academic point of view, the presence of the classical metabolic findings of hyperparathyroidism in association with metastatic malignancy is so interesting that the following case is briefly recorded.

Case No. 5. Hypernephroma with Solitary Metastasis to Bone Simulating Hyperparathyroidism

P. / (M.G.H. 57634) a 50 year old Greek, was followed at the Massachusetts General Hospital from June 1937 until his death and autopsy in August 1940. He had a small hypernephroma of his right kidney with a single inoperable metastasis which involved his right ilium and sacrum (see Fig. 44). Because his serum phosphorus and calcium values were those of hyperparathyroidism he was explored with that incorrect diagnosis in 1937, three normal parathyroids were found, the fourth normal gland being found in the anterior mediastinum at autopsy in 1940. Not only did he have a high serum calcium and a low serum phosphorus level (see Table 1) but these values decreased to normal after a course of x-ray irradiation of the metastatic lesion, only to return to the pre irradiation abnormal values after the effect of the therapy had worn off. Subsequent x-ray irradiation had less effect on the blood values. The calcium excretion in the urine was markedly increased when the serum calcium was high and returned to normal when the serum calcium became normal.

The chemical and metabolic findings, therefore, were those of hyperparathyroidism. The authors have no explanation for the consistent hypophosphatemia in this case. Did the tumor produce a parathyroid hormone like substance?

(3) Other Bone Diseases

There is a large group of other conditions which involve bone which might occasionally be mistaken for osteitis fibrosa generalisata. These cannot be separately discussed. They include lymphoma, benign meta-

stasizing hemangioma, Gaucher's disease, xanthomatosis, chronic radium poisoning, and renal osteitis fibrosa generalisata (see below under 'Secondary Hyperparathyroidism', p 115)

TABLE 1

Effect of Irradiation of Bone Metastasis on the Serum Calcium, Phosphorus, Alkaline Phosphatase and Protein Values in a Patient with Hypernephroma (Case No 6)

Date	Serum			
	Calcium	Phosphorus	Alkaline Phosphatase	Total Protein
	mg %	mg %	Intl. U.	gm. %
6/25/37	13.5	2.6	3.5	6.4
6/30/37	13.1	3.0	4.7	7.1
7/3/37	Parathyroid Exploration			
7/9/37	12.9	3.0	—	—
11/7/37 to 11/23/37	2400 Roentgen Units of Irradiation			
2/3/38	9.2	3.3	4.8	7.2
7/9/38	11.1	3.2	—	7.8
8/24 to 8/29/38	1200 Roentgen Units of Irradiation			
10/22/38	12.9	3.0	—	—
12/10/38	13.1	3.1	—	—
12/12 to 12/24/38	1600 Roentgen Units of Irradiation			
12/21/38	12.8	2.5	4.1	—
1/14/39	13.5	2.6	6.6	—
2/11/39	12.0	2.6	5.5	—
4/22/39	13.7	2.8	4.8	—
6/10/39	14.0	2.9	5.8	—
9/27 to 10/5/39	2100 Roentgen Units of Irradiation			
12/27 to 12/30/39	1200 Roentgen Units of Irradiation			
5/9/40	11.1	4.2	12.0	—
7/24/40	12.8	2.0	4.6	—
8/9/40	12.8	2.0	4.4	—
8/18/40	Died			

(4) Other Conditions Associated with Hypercalcemia

Three causes for hypercalcemia other than hyperparathyroidism have already been discussed, namely, multiple myeloma, metastatic malignancy,

and rapidly developing osteoporosis in children. These are several additional causes, other than a faulty chemical determination which is the commonest. These include vitamin D poisoning, Boeck's sarcoid, an as yet unreported syndrome resulting from a prolonged and excessive intake of milk and alkali, and possibly hyperventilation.

A. *Hypervitaminosis D** ("Vitamin D Poisoning")

The administration of large doses of vitamin D in animals results in metastatic calcification involving the kidneys, bronchi, alveoli of the lungs, mucous membrane of the stomach, blood vessels, and other tissues. Essentially the same pathological picture has been reported in patients who have received excessive doses (circa 150,000 units per day or more) of vitamin D [Freeman, Rhoads, and Yeager (1946), Kaufman, Beck, and Wiseman (1947)]. Periarticular calcification has also been described in man and may be reversible.

The clinical manifestations include symptoms due to hypercalcemia *per se* (anorexia, lethargy, constipation, etc.), polyuria and polydipsia, albuminuria, hyposthenuria, impaired renal function, hypercalcemia, and hyperphosphatemia. There have been cases where the hypercalcemia was not accompanied by hyperphosphatemia, indeed, some cases even have hypophosphatemia (*vide infra*).

The mechanism of the disorder is not entirely clear. There are two schools of thought: one which considers the disorder a poisoning, the other which believes it to be a hypervitaminosis [Tumulty and Howard (1942)]. The former school invokes a mysterious toxic property of vitamin D which is thought to cause tissue necrosis and subsequent calcification. The authors would sooner ascribe the manifestations to an excess of one or both of the two known actions of vitamin D: (1) to increase calcium absorption from the gastrointestinal tract, and (2) to increase phosphorus excretion in the urine (*see page 133*). They further believe that the tissue necrosis is secondary to the precipitation of calcium phosphate in the tissues.

The most probable sequence of events of an excess of the first action of vitamin D is: (1) increased calcium absorption, (2) increased serum calcium level, (3) decreased parathyroid activity, (4) decreased urinary phosphorus excretion, (5) increased serum phosphorus level, (6) supersaturation of the blood with respect to calcium phosphate (*see high calcium and high phosphorus levels*), and (7) precipitation of calcium phosphate at abnormal sites (metastatic calcification). The probable sequence of events of an excess of the second action of vitamin D is the same as that which follows excessive parathyroid hormone (*see Parathyroid Poisoning, page 77*).

* See footnote, page 122 for types of vitamin D.

Since it is probably the first of the above two properties of vitamin D which plays the chief role in hypervitaminosis D, and since you can not have marked calcium absorption if there is very little calcium to absorb, the most important therapeutic indication in vitamin D poisoning would seem to be a low calcium intake. This measure would eliminate all of the sequelae of the first action of vitamin D including the hyperphosphitemia, but would not affect the sequelae of the second action of vitamin D. From this it follows that a patient on a low-calcium intake receiving an excess of vitamin D might exhibit hypercalcemia and hypophosphatemia and thus simulate hyperparathyroidism. Fluids should, of course, be forced, and given parenterally if necessary. In the presence of a high serum phosphorus level one might administer a low phosphorus diet and also aluminum hydroxide to decrease the absorption of phosphorus from the gastrointestinal tract. The patient should be mobilized as much as possible to avoid superimposing atrophy of disuse (see page 147) and thus increasing the serum calcium and phosphorus levels [Tumulty and Howard (1942)]

B Boeck's Sarcoid

Since there may be bone changes (see Fig. 45), high serum phosphatase levels, hypercalcemia, hypercalcuria, and kidney stones associated with Boeck's sarcoid, this condition may in rare instances be mistaken for hyperparathyroidism.

The chemical findings in eleven cases were studied by Harrell and Fisher (1939). These authors found elevated serum calcium values in five of the eleven cases, the level in one patient being 14.8 mg per 100 cc. The hypercalcemia, when present, was not associated with a hypophosphatemia, it, furthermore, was not confined to cases with bone disease. Hyperproteinemia and hyperglobulinemia were almost constant findings. However, the serum proteins were not sufficiently high to explain the elevated serum calcium values. Moreover, in a case studied by the authors (*vide infra*) a markedly increased calcium excretion in the urine was noted which indicates that at least part of the elevation in the serum calcium value is due to an increase in the ionized calcium fraction as opposed to the calcium proteinate fraction. Harrell and Fisher also found elevated serum phosphatase levels, which again did not correlate with the degree of bone disease.

In some unpublished metabolic studies on a classical case of sarcoid (A. M., M. G. H. 252484) it was found that the hypercalcuria was not materially altered when the calcium intake was increased from 344 to 297 mg per day. Accordingly, a markedly negative calcium balance on the low calcium intake was changed to a slightly negative calcium balance on the high calcium intake. These findings are interpreted as evidence that the disordered calcium metabolism is the result not of bone disease *per se*

but of the disordered blood chemistry. In this respect sarcoid resembles hyperparathyroidism.

A most instructive case, which has not heretofore been published, was studied at the Massachusetts General Hospital Clinic.

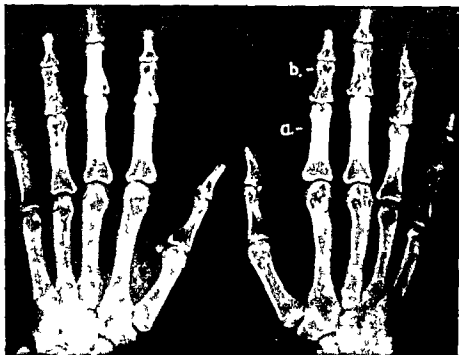


Fig 45 X ray Film of Hand in a Case of Sarcoid to Illustrate Bone Lesions

Note punched out areas areas of coarse trabeculation absence of joint involvement and normal contours of the bone a—normal bone b—sarcoid lesion (The authors are indebted to Dr G T Harrell Jr of Duke University for this illustration.)

Case No. 6 Boeck's Sarcoid with Hypercalcemia and Nephrolithiasis, Parathyroid Exploration and Partial Resection

F. L. (M.G.H. 30032), was first seen in 1934 at the age of 21. She had had weakness of two years' duration, twenty one pounds loss in weight, pyelitis for over one year, a left nephrectomy for kidney stones, and a right pyelotomy for the removal of a kidney stone. Physical examination was non-contributory except for an enlarged spleen. X rays of the lung showed what at that time was considered to be miliary tuberculosis; no bone lesions were demonstrated in spite of extensive x rays. A stone was present in the right kidney. The pertinent laboratory findings were: albuminuria with a small amount of 'atypical Bence Jones proteinuria', pyuria, bacteriuria, a moderate anemia, a serum protein of 8.0 gm. per 100 cc. without a reversal of the albumin globulin ratio, and a decreased phenolsulphonphthalein excretion. The serum calcium was 13.8 mg. per 100 cc.,

the serum phosphorus 3.2 mg per 100 cc, and the serum phosphatase 11.7 Bodansky units. On a calcium intake of 320 mg per three-day period the patient put out 990 and 1020 mg in each of two three-day periods, respectively (normal circa 190 mg). In spite of the fact that the diagnosis seemed far from certain in view of the lack of hypophosphatemia, a parathyroid exploration was performed with the finding of three normal parathyroid glands. Two of these were removed and the third was biopsied. The serum calcium fell promptly to 9.8 mg per 100 cc, the serum phosphorus rose to 5.0 mg per 100 cc. The hypercalcemia gradually returned, however, the level reaching 12.4 mg per 100 cc in four months.

The patient made an unexpectedly good convalescence. The milary lesions in the lung gradually disappeared as did the enlargement of the spleen. Her weight and strength came back and with this her hypercalcemia gradually disappeared. The stone was removed from her kidney, her urinary infection was cleared up with mandelic acid, she completely regained her health and was married in 1940.

With our knowledge at its present state the differentiation of sarcoid from hyperparathyroidism should offer little difficulty. The absence of hypophosphatemia, the absence of generalized decalcification, and the hyperproteinemia in sarcoid are differential points. The bone lesions in sarcoid, furthermore, are mostly confined to the hands and feet. They consist of circumscribed lesions of coarse trabeculation and sharply punched-out, small, cyst-like areas (see Fig. 45).

C *Syndrome Resulting from Prolonged and Excessive Intake of Milk and Alkali*

There is an interesting group of cases, as yet unpublished, in which the etiological factor seems to be prolonged and excessive intake of milk and alkali. These cases have been observed by Dr. John Lager Howard at Johns Hopkins Hospital, by Dr. George W. Thorn at Peter Bent Brigham Hospital, and by Dr. Charles H. Burnett and others of our clinic at the Massachusetts General Hospital. The clinical features are: 1) hypercalcemia without hypercalciuria, 2) a normal or high serum phosphorus level, 3) impaired renal function with retention of non-protein nitrogen, decreased excretion of phenol-sulphonphthalein, and fixed specific gravity of the urine, 4) conjunctival calcium deposits and "band keratitis" (see page 67), and 5) lowering of the serum calcium level with clinical improvement when the patient is placed on a low-calcium diet.

(II) *Treatment of Primary Hyperparathyroidism*

(1) *Non-Surgical Treatment*

Except for the treatment which one applies in getting a patient ready for surgery, the authors do not believe that there is any justifiable non-surgical treatment.

To be sure, as discussed above, one can prevent a negative calcium balance in hyperparathyroidism and even produce a strongly positive one by giving the patient a high calcium intake (see Fig 31, p 68). The authors have seen such treatment prevent further bone disease and, in the course of years, improve the bone disease. In the final analysis however it is the kidney complications of hyperparathyroidism which are the serious ones and the irreversible ones. A high calcium intake does not prevent these, if anything, it favors them. Furthermore, the hypercalcemia persists in patients on a high calcium intake and with it the symptoms dependent on the hypercalcemia *per se* (see p 65).

The authors have also experimented with a high phosphate diet. By administering to a patient with hyperparathyroidism a very high phosphate intake one can elevate the depressed serum phosphorus level, lower the elevated serum calcium level, and decrease the increased calcium excretion in the urine (see Fig 8, p 21). However such therapy causes a tremendous increase in the already high phosphate excretion in the urine and must materially increase the danger of nephrolithiasis and nephrocalcinosis. It is not to be recommended.

While the patient is awaiting operation or is being prepared for operation it is important that "parathyroid poisoning" (see p 77) be averted and that further kidney damage be prevented. Unnecessary ingestion of calcium and phosphate should therefore, be avoided which, from a practical point of view, means that milk and cheese should be eliminated from the diet. Fluids should be forced. If there is any suggestion of parathyroid poisoning or renal insufficiency, intravenous saline should be administered.

(2) X ray Irradiation of Parathyroid Glands

In spite of favorable reports from other clinics the authors have had no success with this means of therapy nor are they convinced by the published reports [Merritt and McPeak (1934), Cutler and Owen (1934), Anspach and Clifton (1939), and Jacob, King and Bailey (1939 and 1940)]. The authors have searched for one case of unquestionable hyperparathyroidism with the classical blood chemistry findings in which normal findings were restored following irradiation therapy and persisted over a reasonable period of time. The fact that a patient with some bone lesions showed symptomatic or even x ray improvement does not impress the authors since this can be obtained in hyperparathyroidism by a high calcium diet alone (*vide supra*). One of the authors (T. A.) has communicated with the cited proponents of x ray therapy with the exception of Jacob *et al* in the hope that they could furnish further evidence which would be convincing of the efficacy of this therapy in at least one case, that additional evidence which was obtained actually weakened the case for x ray therapy. Thus

of the six cases reported by Merritt and McPeak (1934), case 3 came nearest to fulfilling the criteria outlined above. However, in a personal communication Dr Merritt states that the blood chemistry in this patient did not remain normal after therapy. Cutler and Owen's case (1931) died; the microscopic findings at autopsy were reviewed by one of us and Dr Benjamin Castleman, what might have been the remnants of a parathyroid adenoma were present. However, the bone sections showed osteitis fibrosa; the remaining parathyroids were hyperplastic, and there was marked calcinosis of the kidneys. It was clear that at death the patient had renal osteitis fibrosa—that the renal disease was on the basis of a parathyroid adenoma which was destroyed by x ray is a distinct possibility but not proven. Anspach and Clifton's (1939) case 2 which was quite suggestive apparently was not cured by irradiation and was still suffering from symptoms which somewhat suggest renal rickets to Dr Anspach. The facts in Jacob *et al*'s case (1939) (1940) with the persistence of hypercalcemia following irradiation and the inability to demonstrate a parathyroid tumor at autopsy could hardly be construed as evidence for the efficacy of this form of therapy.

The authors have given x ray irradiation a thorough trial both in cases due to adenoma and in cases due to hypertrophy. Irradiation has been forced to the limit of tolerance—one patient developing an esophagitis as a result. The authors have controlled their observations with extensive metabolic studies and with histological studies of the irradiated parathyroid tissue which was subsequently removed. In no instance has a definite effect on the degree of hyperparathyroidism been noted. In the authors' opinion, therefore, x ray irradiation should be used as a last resort if tried at all.

(3) Surgical Treatment

The authors believe that surgery is the only satisfactory treatment of primary hyperparathyroidism. The subject divides itself into two parts (a) the uncovering of the parathyroid pathology, and (b) the decision as to what tissue to remove and what tissue to leave behind.

It is not proposed here to enter into a detailed discussion of surgical technique. The reader is referred to papers by Walton (1931), Churchill and Cope (1936) and Cope (1941). The authors, however, cannot resist putting in a few words.

In the first place, as to choice of surgeon—a good thyroid surgeon is not enough. The finding of a parathyroid tumor may be very simple or very difficult. The operation should not be undertaken by a surgeon who has not made a special study of the appearance and location of normal parathyroid glands of their differentiation from small lymph nodes and

collections of fat, *et cetera*. Much mischief has been done by the 'let's have a look' approach to the problem. There is no time like the first operation to uncover a small adenoma. Once the neck is filled with scar tissue, the problem becomes much more difficult. As in all surgery the second fifty operations for any operator are much simpler than the first.

The not infrequent occurrence of parathyroid adenomata in the mediastinum creates an interesting surgical problem which has been discussed by Cope (1941). Of the first 60 cases of hyperparathyroidism at the Massachusetts General Hospital 11 had tumors in the anterior mediastinum and 5 in the posterior mediastinum. Statistically, these figures mean nothing

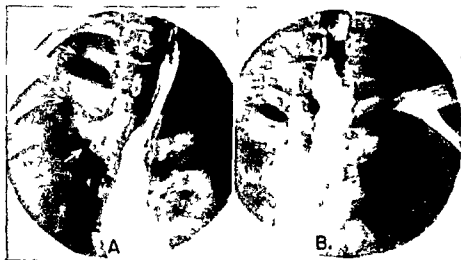


Fig. 46 Demonstration of Parathyroid Tumor by Barium in the Esophagus
 A—esophagus displaced to left by tumor; arrows delineate outer edge of tumor
 B—esophagus in normal position after removal of tumor

since of 9 cases explored before they were referred to this clinic, 6 had adenomata in the anterior mediastinum and 1 in the posterior. Even when these cases are deleted from the series however, 9 of 49 adenomata were in the mediastinum, 5 (10 per cent) being in the anterior mediastinum, and 1 (8 per cent) being in the posterior mediastinum.

The reason for the not infrequent occurrence of parathyroid glands in close proximity to the thymus becomes apparent when one goes back to the embryology [Weller (1933), Norris (1937)]. The lower parathyroids develop from the third branchial clefts in close proximity to the primordia of the thymus gland. As the thymus tissue moves downward to its position in the anterior mediastinum, the parathyroid tissue descends with it. Weller (1933) has called this pair of parathyroid glands the 'parathymus glands'. The majority of these parathymus glands are dropped off oppo-

site the lower pole of the thyroid, sometimes, however, a parathyroid gland goes with the thyroid beyond the lower pole of the thyroid and is deposited in the mediastinum. Such a parathyroid gland may actually be within the thyroid capsule. It is of historic interest that Captain Charles Martell, the first case of hyperparathyroidism to be diagnosed in this country and the second in the world, had his tumor in the anterior mediastinum, from which it was removed by Dr. Edward D. Churchill during the seventh parathyroid exploration.

Before the operation is undertaken, an attempt should be made to locate the tumor by x-ray. In the first fifty cases at the Massachusetts General Hospital this was accomplished in three instances and could have been done in one or two others. In addition to taking the usual plates, one should fluoroscope the patient while having him swallow barium and look for displacements of the esophagus. Tumors not infrequently lie in close proximity to the esophagus (see Fig. 16). Whether or not the new planograph technique will be of value in locating substernal tumors has not yet been established.

Once the parathyroid pathology has been uncovered, the question arises as to what to do about it. The decision will depend on whether the pathology is a single adenoma, multiple adenomas, or parathyroid hypertrophy. Furthermore, in deciding how much tissue to remove, one will be influenced by the state of the remaining normal parathyroids, by the height of the serum phosphatase level and by the level of the kidney function.

Whether one is dealing with tumor or hypertrophy can usually be decided by the experienced operator from the gross appearance of the gland [Cope (1911)], in any case a good frozen section will readily settle the question because of the tremendous increase in the size of the cells in the hypertrophy type of pathology. Then, if there has been no damage to parathyroid tissue from previous operations, if the serum phosphatase is not elevated and if there is no renal insufficiency, one would remove all of a single adenoma and all of two adenomas. To be sure, if one found a single adenoma and did not know whether there was another, one would be justified in stopping the operation after one side of the neck had been explored and in waiting to see if the patient made a complete recovery. This would be a better plan of procedure than "taking a quick look" on the other side, which probably would not reveal a second adenoma and which would make a second operation more difficult. If the parathyroid enlargement turned out to be the result of hypertrophy, the surgeon should then attempt to uncover all four parathyroid glands, he should remove three of them *in toto* and leave behind with a good blood supply about 200 mg. of the fourth [Albright, Sulkowitch, and Bloomberg (1935)].

Needless to say, if the patient has had previous operations on the neck

with an unknown amount of destruction of the normal parathyroid tissue, one would probably not resect a parathyroid adenoma completely unless one could demonstrate some normal remaining parathyroid tissue. Furthermore, as will appear in the following section, if a patient has marked bone disease and a high serum phosphatase level, the complete elimination of the state of hyperparathyroidism at one sitting will lead to severe post-operative tetany. It has been, therefore, the policy in the Massachusetts General Hospital Clinic in such cases to remove only a part of the parathyroid tumor at the first operation in order to prevent severe post-operative tetany,* if the state of hyperparathyroidism recurs the remainder of the tumor can be removed at a second operation. Surprisingly enough several cases have gone over five years without a second operation being necessitated. Finally, as discussed under Secondary Hyperparathyroidism (see p 115), in the presence of kidney damage with a tendency to phosphate retention one removes less parathyroid tissue than one otherwise would.

(I) *Post Operative Course and Treatment*

The discussion under this heading will be divided into (a) post operative course when disease is not complicated by osteitis fibrosa generalisata, and (b) post operative course when disease is complicated by osteitis fibrosa generalisata.

(1) *Post Operative Course if No Osteitis Fibrosa Generalisata*

If the hyperparathyroidism is not complicated by bone disease one expects the same metabolic adjustments following the removal of the tumor as occur after cessation of parathyroid hormone administration to a normal individual. Such is the case. The serum calcium falls to normal (but not below normal) within one to four days, the serum phosphorus in most instances promptly rises although this is not a constant finding (see case No 7). In my event there is an immediate fall in both the calcium and phosphorus excretions in the urine; moreover the decrease in the phosphorus excretion is greater than can be explained by the decrease in the calcium excretion on the assumption that the changes represent diminished mobilization of calcium phosphate from the bone (ratio of calcium to phosphorus approximately 2:1). It is evident therefore, even in those cases where the serum phosphorus does not promptly rise, that phosphorus is collecting somewhere other than as calcium phosphate in the bones.

Some interesting and heretofore unpublished data were obtained on a

* With improved knowledge of therapy we have become less conservative as regards the removal of a parathyroid adenoma and in fact at the first operation

patient whose history is presented in more detail elsewhere [see Albright, Bloomberg, Castleman, and Churchill (1934) case 16]

Metabolic Study No 1

Case No 7 Hyperparathyroidism due to Hypertrophy of All Four Parathyroid Glands Without Bone Disease and With Renal Calculi, Effect of Parathyroid Operation on Calcium and Phosphorus Metabolism

T F (M G H 333011), a 26 year old male, presented no evidence of bone disease a normal serum phosphatase level a history of renal colic, and no impairment of renal function During this experiment which started two days before and continued until four days after the parathyroid operation, urine was collected in four hour periods, at the beginning of each period the patient received 16 ounces of milk—his only food or fluid The urine for each period was analyzed for calcium and phosphorus The operation was done under local anesthesia so as not to interfere with the metabolic studies The pathology turned out to be parathyroid hypertrophy, only two of the parathyroid glands being removed at this operation This was not quite sufficient to return the patient to a state of isoparathyroidism, but as will be seen there was a very definite lowering of the degree of hyperparathyroidism, a second operation was performed later

In Fig 47, which shows the metabolic data, it will be seen that in the first four hours after the removal of the parathyroid tissue there were definite decreases in the urinary phosphorus excretion and the serum calcium level The main purpose of this illustration, however, is to point out that the fall in the urinary phosphorus excretion is out of proportion to that in the urinary calcium excretion In Fig 47 the scale for the urinary phosphorus excretion is twice that for the urinary calcium excretion so that the fluctuations of these two variables on the chart should be equal if the changes were dependent on decreased calcium phosphate mobilization from the bones (ratio of calcium to phosphorus circa 2:1) It will be noted that in spite of there being no post-operative rise in the serum phosphorus level, the decrease in the urinary phosphorus excretion was proportionately much greater than that in the urinary calcium excretion If one assumes probably correctly, that there was no significant change in the fecal excretion, one must conclude that phosphorus was being retained somewhere other than in bone tissue, possibly in intracellular fluid

(2) Post Operative Course in the Presence of Osteitis Fibrosa Generalisata

If the hyperparathyroidism is complicated by osteitis fibrosa generalisata the removal of the entire cause for the disease in one operation will almost invariably be followed by a fall in serum calcium to tetany levels Furthermore, the serum phosphorus instead of rising will fall, and the elevated serum phosphatase will actually rise further Calcium and phosphorus will practically disappear from the urine

Fig 48 was constructed to emphasize that the serum calcium level falls below normal only in those cases which pre-operatively have osteitis fibrosa generalisata and hence high serum phosphatase levels Incidentally, the

figure also demonstrates that the cases with bone disease are not necessarily the ones with the greatest degree of hyperparathyroidism as judged by the heights of the serum calcium levels.

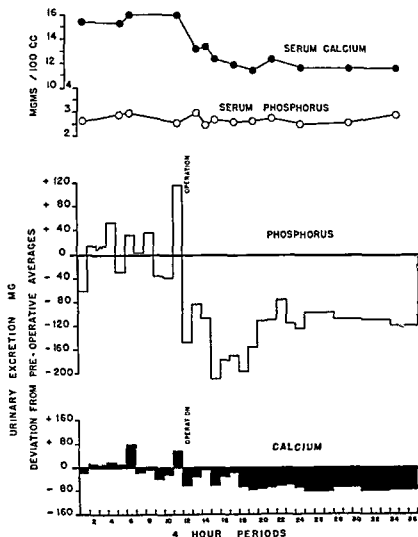


Fig 17. A Comparison of the Decrease in the Urinary Phosphorus Excretion with the Decrease in the Urinary Calcium Excretion Following the Removal of Parathyroid Tissue in a Patient in Whom the Operation Was Followed by a Marked Fall in the Serum Calcium Level Without a Rise in the Serum Phosphorus Level

For details of experiment, see text (Patient T F, M G II 333011.)

To understand why, in the presence of osteitis fibrosa generalisata, the serum calcium falls to tetany levels, why the serum phosphorus falls, and why the serum phosphatase rises, it is necessary to focus one's attention

on the changes which are occurring in the bones. The subject is so important for the post-operative care of such patients that the authors go into it in some detail. Some metabolic and bone histologic data obtained on a

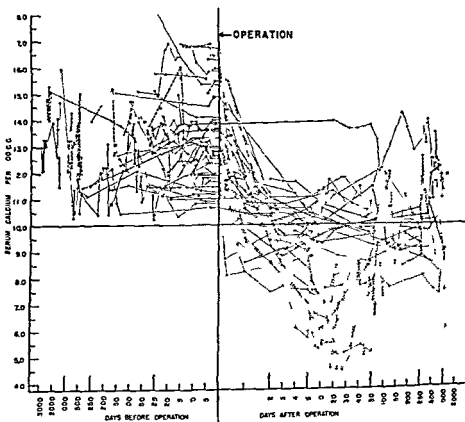


Fig 48 Pre and Post Operative Serum Calcium Values in 35 Proved Cases of Hyperparathyroidism

The values connected by dotted lines are on patients with high serum phosphatase levels. Asterisks denote points at which secondary parathyroid operations were performed. Note that cases with high phosphatase levels and therefore with bone disease are distributed evenly at various levels of hypercalcemia pre-operatively; however, note that these cases all developed hypocalcemia post-operatively. For further discussion, see text. [From Albright, Sulkowitch and Bloomberg (1937)]

patient several years ago in conjunction with Dr. Walter Bauer and Dr. Granville A. Bennett are reported. These data were presented briefly before the Association of American Physicians in May, 1934 by Dr. Walter Bauer but have never been published.

Metabolic Study No. 2

Case No. 8 Hyperparathyroidism with Osteitis Fibrosa Generalisata and Nephrocalcinosis, Removal of Parathyroid Adenoma, Serial Bone Biopsies

J. C. (MIG H 327913), a male aged 33 years, complained of pain in his legs, weakness, and loss of weight. The diagnosis of hyperparathyroidism was made by Dr. Alice Ettinger and Dr. Heinz Magendantz (1934) when their roentgenographic studies revealed fine calcium deposits in the kidney pyramids (see Fig. 49) and the patient was referred to the Massachusetts General Hospital for study [Albright, Baird, Cope and Bloomberg (1934)]. His serum calcium was 17.0 mg



Fig. 49 Case No. 8 Hyperparathyroidism with Nephrocalcinosis. X-ray Films of Kidneys to Show Fine Calcium Deposits

per 100 cc., his serum phosphorus 3.0 mg. per 100 cc., and his serum phosphatase 22 Bodansky units. Renal function tests showed definite kidney impairment. A single parathyroid tumor was found and removed on March 25, 1933 following which the patient developed rather severe tetany from which he gradually recovered. He proceeded to gain strength and weight and was considered much better until 1936. At this time the renal insufficiency became rapidly worse and he died in uremia on May 2, 1936.

The studies include metabolic data before and after the operation and bone biopsies at the time of the operation, 8 days after the operation, and 119 days after the operation.

The metabolic data are shown in Fig. 50. One notes the rapid fall in serum calcium, the slight but definite fall in the serum phosphorus, and the slight rise

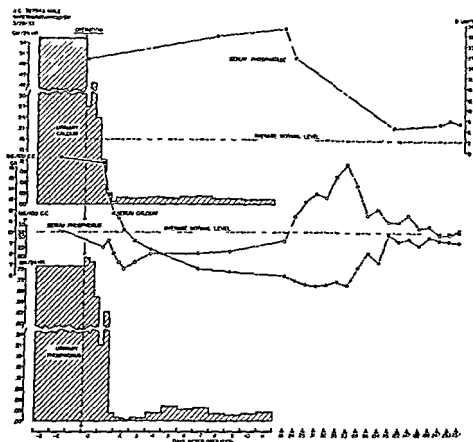


Fig 50 Metabolic Data Showing Effect of Removal of Parathyroid Adenoma on Urinary Calcium and Phosphorus Excretions and on Serum Calcium, Phosphorus and Alkaline Phosphatase Levels in a Patient with Hyperparathyroidism and Osteitis Fibrosa Generalisata

The urinary values were carried out on a 3-day period before operation, on 8 hour periods for the first three days after operation, and on 24 hour periods during the third to the eleventh post-operative days. The scales for the urinary calcium and phosphorus excretions are the same, that of the phosphorus not being twice that of the calcium as in most of the charts.

Especially to be noted are the rapid fall in both the calcium and phosphorus urinary excretions; the fact that the serum phosphorus level fell as well as the serum calcium level; and the slight but definite rise in the serum alkaline phosphatase level. Further to be noted is the gradual return of the serum levels to normal. Attention is also called to the fact that in spite of a fall in the serum phosphorus level, there is a relatively much greater fall in the urinary phosphorus excretion than in the urinary calcium excretion (0.75 gm per 24 hours of phosphorus as compared with 0.51 gm of calcium). These findings are in agreement with those of Fig 47.

in the serum phosphatase after the operation together with the immediate and almost complete disappearance of both calcium and phosphorus from the urine

The reason for these changes is apparent when one studies the bone biopsies. In Fig. 51 photomicrographs of three biopsies are reproduced together with schematic interpretations. In the biopsy taken at the time of the operation one notes the expected findings: viz. bone surfaces about equally divided between bone forming and bone resorbing surfaces, many osteoclasts on bone resorbing surfaces, many osteoblasts on bone forming surfaces, and no increase in width of osteoid seams indicating that matrix which is being deposited by osteoblasts is being immediately calcified. It will be noted in the schematic diagram that the source of calcium and phosphorus for the osteoblastic surfaces is derived from the osteoclastic surfaces. Now, when one turns to the biopsy taken 8 days after the operation, one notes the complete disappearance of bone resorbing surfaces and of osteoclasts, the covering of all surfaces with osteoblasts, and the presence of wide osteoid seams. It is quite clear that the little calcium and phosphorus that was in the body fluids has been mostly sucked into the bones; that there is now no source of supply of calcium and phosphorus with which to build bone, and that the osteoid seams are therefore wide. The elevation in the serum phosphatase level, furthermore, may very well be due to the fact that all surfaces rather than only half the surfaces are now covered with osteoblasts. It will be noted that both the blood chemical and histological findings at this stage indicate osteomalacia. In the biopsy taken at 119 days, the findings have reverted almost to the normal state of affairs.

The importance of these observations, from a clinical point of view, has to do with the treatment of the post operative tetany. Of course, the most important thing in the treatment of this condition is its prevention. To this end, it used to be the practice in this clinic not to eradicate completely the state of hyperparathyroidism at one operation in patients with very high serum phosphatase levels. It should be emphasized, furthermore, that the tetany encountered after removal of a parathyroid tumor may be much more severe than that ever seen after removal of parathyroid glands in the course of a thyroid operation. The treatment, likewise, is very much more difficult. It may at first seem surprising that it is impossible to elevate the serum calcium with parathyroid hormone. Just why this is so indeed, is not altogether clear. As pointed out above, the cause of the tetany is not hypoparathyroidism by osteomalacia. It would seem that, once the trabeculae are all surrounded with osteoblasts, the bone tissue is insulated, as it were, and cannot give up its calcium and phosphorus to body fluids (see p. 206). It is also highly unlikely that A.T.10 or vitamin D would be of benefit in raising the serum calcium level. Both of these agents increase calcium absorption from the gastro-intestinal tract. This, however, is not the difficulty. The problem is to keep the calcium in the blood from going into the bones. Such a patient should be put on a low phosphate intake. After all, the calcium leaves the blood as calcium phosphate to be precipitated in the bones. The less the phos-



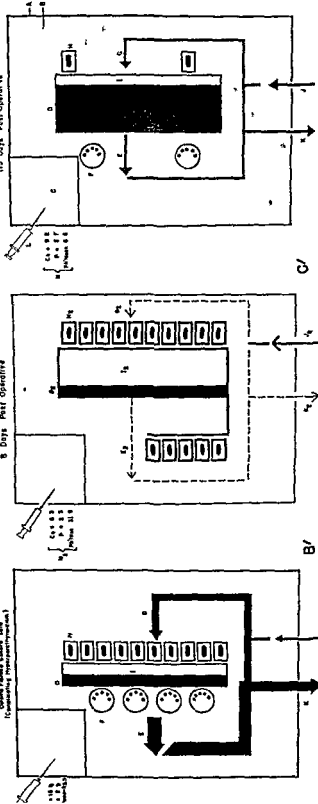


Fig. 31 Bone Biopsies at Time of Removal of Parathyroid Adenoma (A), Eight Days Later (B), and One Hundred and Nineteen Days Later (C), with Schematic Interpretive Diagrams (A', B', C') for 1 each of the Biopsies Respectively

Diagrams follow same scheme as those in Fig. 30, p. 82

A a—osteoclast, b—osteoblast, c—fat tissue, d—bone trabeculae, e—osteoid seam. Note that bone trabeculae do start somewhere and go somewhere in contrast to Paget's disease (see Fig. 147 A, p. 288), note that bone surfaces are about equally divided between bone destroying surfaces and bone forming surfaces (see A' also), note that osteon 1 which is formed is calcified so that osteoid seams are narrow -e, A'-I)

3 Lettering follows same scheme as in A. Note complete disappearance of osteoclasts (see also B'). Note that almost all surfaces now are eroded with osteoblasts which may account for rise in serum phosphatase, note that osteoid which is formed is not completely calcified so that the osteoid seams are wide (B-e B'-I)

2 Lettering again the same as in A, g—fat tissue. Note that bone tissue has now returned almost to normal. There is very little evidence of bone formation or bone destruction. Serum phosphatase has fallen from a high level of 31.9 (B') to 0.6 Bodansky units (C') [From published data of Dr. Granville A. Bennett, Dr. Walter Bauer, and one of us (T. A.)]

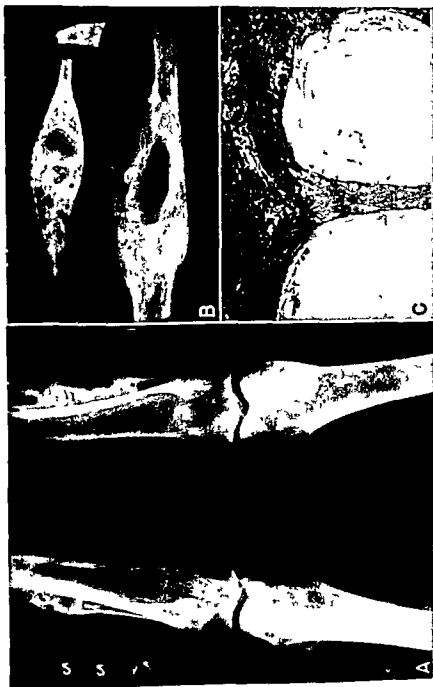


Fig 52 Effect of Removal of Parathyroid Tumor on Bone Lesions

(A) X ray of humerus and tibia before removal of tumor, (B) X ray of same bones at autopsy 27 months after parathyroidectomy, and (C) microscopical section of two cysts (Patient N. B., No. 11, 207624)

phate, the less the precipitation of calcium into the bones. Hence, the patient should be on a high calcium, low phosphorus regimen. This means no milk or cheese. In the authors' experience the only successful way to deal with the situation is by the giving of a continuous intravenous infusion containing calcium gluconate or calcium lactate. Thus in one patient (L K, M G H 344332) who had very severe tetany with generalized convulsions 100 cc of ten per cent calcium gluconate in 1 000 cc of five per cent glucose were administered intravenously by slow drip daily

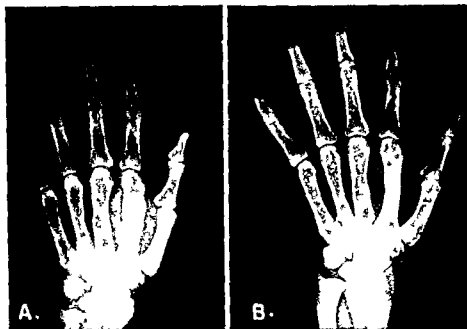


Fig 53 X Ray Films to Illustrate Effect of Extirpation of Parathyroid Adenoma on True Bone Cysts as Opposed to "Pseudo Bone Cysts"

(A) X ray at time of operation, (B) X ray 4 1/2 years after operation (patient M G H 310023). Note that cystic appearing lesion in third metacarpal bone remains essentially unchanged which indicates that it was a true cyst, while cystic appearing lesion in second metacarpal bone has been turned into dense bone which indicates that it was a "pseudo-cyst"

Of course, in time, weeks to months, "the hungry bones" become filled up with calcium and less subject to stresses and strains, the serum phosphatase falls, and the hypocalcemia and tetany disappear

(3) Healed Osteitis Fibrosa Generalisata

The end state of the skeletal lesions after removal of a parathyroid tumor is not normal bone, at least not within the first five years. In the first

place true bone cysts (i.e. those containing fluid) always remain bone cysts. Their walls calcify but it is hard to see how they themselves could fill in (see Fig. 52 and 53). In contradistinction pseudo-bone cysts (i.e. those such as osteoclastomata containing fibrous tissue) become reorganized and eventually filled in with bone. Then it must be remembered that although the bones are decalcified in osteitis fibrosa generalis, the

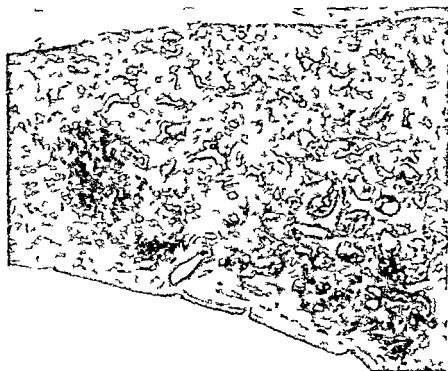


Fig. 54 Healed Osteitis Fibrosa Generalisata in a Case of Hyperparathyroidism. Cross-Section of Skull.

Patient N. B. (M.G.H. 307621) died 2½ months after parathyroidectomy. Note that instead of an inner and an outer plate with diploë in between there is now merely a solid mass of bone tissue.

alivata, the framework on which to build bone is actually increased. Thus the marrow spaces are crowded out by tissue which is forming bone matrix. Now when the parathyroid tumor is removed and all bone destruction is stopped, the repair processes proceeded a great deal further than to the restitution of the normal amount of bone tissue (see Fig. 53). One encounters a very dense skeleton: the skull, for example, instead of consisting of two plates with diploë between is composed of a solid mass of bone (see Fig. 54).

(A) *Definition*

By secondary hyperparathyroidism is meant a state of affairs where because of some modifying circumstance more parathyroid hormone is needed by the body than under normal circumstances. The condition probably occurs under the following circumstances: calcium deprivation due to diet, pregnancy, lactation, rickets and osteomalacia and chronic nephritis. Only the last two of these conditions will be discussed here.

(B) *Parathyroid Pathology in Secondary Hyperparathyroidism*

One finds of course hyperplasia of the parathyroid tissue in secondary hyperparathyroidism. Clinically the condition reaches its most marked degree in cases of long standing chronic renal insufficiency. The histological characteristics have been described by Castleman and Mallory (1930). The glands vary in size from perfectly normal sized glands up to ones which are almost 100 times normal size. Except in rare instances however they are decidedly smaller than the glands seen in hypertrophy of the parathyroid glands (*vide supra* p. 71). Castleman and Mallory listed the following characteristics:

- (a) a decrease or absence of intercellular fat tissue
- (b) a predominance of normally sized chief cells
- (c) an absence of mitoses
- (d) more numerous oxyphil cells than one would expect for the age of the individual and
- (e) a somewhat higher glycogen content of the cells than one would expect in adenomata or in hypertrophy of the parathyroid tissue.

It should be noted that any hyperplastic gland even when not any larger than a normal gland is probably producing very much more hormone since the fat cells are all replaced by epithelial cells.

(C) *Secondary Hyperparathyroidism in Renal Disease*(1) *With Phosphate Retention*

In patients with renal insufficiency in whom there is a retention of non protein nitrogen there is almost always a retention of serum phosphorus. Such individuals at post mortem show an hyperplasia of all four parathyroid glands. In rare instances of long duration the condition may be accompanied by generalized bone disease. In adults this bone disease as far as the authors are aware is indistinguishable from the osteitis fibrosa generalisata associated with hyperparathyroidism and the authors have used the term renal osteitis fibrosa generalisata, in describing this condition [Albright (1936)]. In children before union of the epiphyses one can

counters the same bone changes plus changes in the epiphyses. The authors have seen two cases with bilateral slipped femoral epiphyses in adolescent individuals. Inasmuch as the changes in the epiphyses give an appearance in the roentgenogram similar to that seen in rickets, the condition has been designated "renal rickets." Actually the epiphyseal lesions in renal rickets under the microscope are not those seen in true rickets [Albright, Drake and Sulkowitch (1937)]. Furthermore, it should be remembered that osteitis fibrosa generalisata due to hyperparathyroidism and uncomplicated by kidney damage is not associated with epiphyseal lesions in children (see p 88). Thus, all that can be said is that the bone lesions in "renal rickets" histologically are more like those seen in osteitis fibrosa generalisata than in any other condition, however, they are associated with changes in the epiphyses which do not occur in hyperparathyroidism and which by x ray resemble very closely those seen in true rickets.

It is the authors' opinion (see p 231, and Fig 118, p 233) that the sequence of events leading to the parathyroid hyperplasia is as follows:

- (a) kidney insufficiency,
- (b) phosphorus retention,
- (c) tendency to a low serum calcium level as an adjustment to high serum phosphorus level, and
- (d) hyperplasia of the parathyroid glands to meet this tendency.

Drake, Albright, and Castleman (1937) were able to produce hyperplasia of the parathyroid glands in rabbits by the parenteral injection of phosphates. It follows, therefore, that the phosphorus retention in chronic renal insufficiency would probably be much greater were it not for this compensatory hyperplasia of the parathyroids. Up to this point most investigators are pretty well in agreement.

The next question is: What is the relation of the parathyroid hyperplasia to the bone changes? To those who believe that the parathyroid hormone acts directly on bone tissue the obvious explanation is that the mechanism for the bone disease is the same as in primary hyperparathyroidism. To the other school, which believes that parathyroid hormone acts by first causing a depletion of fluid phosphates, it is difficult to see how any sequence of events which starts with retention of phosphates leads to bone disease. In the authors' opinion the bone disease is not directly connected with the secondary hyperparathyroidism but is entirely dependent on the associated acidosis which is invariably present, in their experience, in these cases. For further discussion of the sequence of renal osteitis fibrosa generalisata see p 231, and Fig 118. The fact that the bone disease responds to measures which overcome the acidosis but not the phosphate retention (unpublished data) is an argument in favor of the authors' point of view.



Fig 55 Renal Osteitis Fibrosa Generalisata X ray Film of Hand Showing Calcium Deposits Around Joints

[From Albright, Drake and Sulkowitch (1937)]

The clinical characteristics of renal osteitis fibrosa generalisata in adults include renal insufficiency which is long standing and severe, nitrogen and phosphorus retention normal or slightly low serum calcium level, severe acidosis with a low CO_2 combining power of the serum and either a high

serum chloride level or a low serum sodium level, arteriosclerosis of the Monckeberg type (medial arteriosclerosis), a high serum phosphatase level, and sometimes calcium deposits around joints. The following case illustrates some of these points



Fig 56 Renal Osteitis Fibrosa Generalisata X Ray Picture of Vertebrae at Autopsy to Show Decalcification and Herniations of Nuclei Pulposi into the Vertebrae [From Albright, Drake and Sulkowitch (1937)]

Case No 9 Renal Osteitis Fibrosa Generalisata, Parathyroid Hyperplasia

F L S (M G H 319407), a 45 year old male died of renal insufficiency. His chief complaint on admission to the hospital was painful swellings of the fingers which were first considered to be gout and were later proved to be due to calcium deposits around the joints (see Fig 55). He had been diagnosed as having "incurable Bright's disease" twenty three years previously.

The important laboratory findings were albuminuria +++ , rare red and white cells and hyaline casts in the urinary sediment, secondary anemia, an elevated non protein nitrogen (120 mg per 100 cc of whole blood), fixation of urinary specific gravity, a very low phenolsulphonphthalein excretion, a high serum phosphorus level (9.8 mg per 100 cc), a slightly low serum calcium level (8.2 mg per

100 cc), a high serum phosphatase level 9.4 Bodansky units), a very low serum carbonate level [11.6 m eq per liter (normal, *circa* 26 m eq per liter)], a slightly high serum chloride [106.1 m eq per liter (normal, *circa* 103 m eq per liter)] and a very low serum sodium [127.2 m eq per liter (normal, *circa* 140 m eq per liter)] These findings were considered to be consistent with a quiescent, chronic glomerulonephritis.

The roentgenogram revealed generalized decalcification, with the "ground glass" skull identical with that seen in the osteitis fibrosa generalisata of hyperparathyroidism (see Fig. 27B, p. 60), and with herniations of the nuclei pulposi through the end plates of the vertebrae (see Fig. 56).

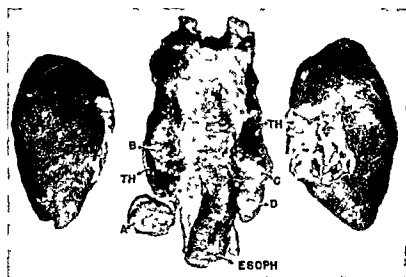


Fig. 57 *Renal Osteitis Fibrosa Generalisata* Photograph of kidneys and Neck Organs at Autopsy

Note marked enlargement of all four parathyroids—A, B, C, and D, and small granular kidneys. [From Albright, Drake, and Sulkowitch (1937)]

At autopsy, all four parathyroid glands were huge (see Fig. 57). The kidneys were very small and granular and again suggested the healed stage of chronic glomerular nephritis, if there is such a thing. The blood vessels showed marked *Mönckeberg's sclerosis*. Histological studies showed typical osteitis fibrosa of the bone (see Fig. 58) and hyperplasia of the parathyroid tissue (see Fig. 24A, p. 52).

Since, according to the authors, acidosis is the cause of the bone disease, the main therapeutic indication is the administration of some alkaline salt, e.g. sodium citrate, in sufficient quantity (*circa* 2 to 3 grams 1 times daily by mouth) to restore the carbon dioxide content of the serum to a satisfactory (*circa* 23 m eq per liter) if not normal level (*circa* 26 m eq per liter). Citric acid can be added to the sodium citrate to make the intestinal contents more acid and increase the absorption of calcium (see p.

234) To be sure, the overcoming of the acidosis by the above therapy in the presence of a low serum calcium level may lead to tetany, this danger in actual experience turns out to be more theoretical than real. Overcoming the acidosis stops the loss but does not lead to a satisfying retention of calcium. This end is attained by administering together with the alkali Vitamin D in large quantities (*circa* 50 000 units daily by mouth) and a calcium salt, e.g. calcium gluconate (*circa* 5 grams 3 times daily by mouth), to assure a high calcium uptake.



Fig. 58. Renal Osteitis Fibrosa Generalisata. Photomicrograph of Bone Biopsy. Note that bone lesion is the same as that seen in osteitis fibrosa generalisata resulting from hyperparathyroidism—see Fig. 51A. [From Albright, Drake, and Sulzowitch (1937)]

As far as the bone disease is concerned the results of the above therapy are most spectacular (unpublished data). Skeletal symptoms are relieved almost at once, and unequivocal improvement by X ray can be demonstrated in about two months. This therapy, of course, does not materially affect the ultimate serious prognosis as regards kidney failure. It is disappointing that neither the anemia nor the kidney function are improved by elimination of the acidosis. Other measures usually employed for the treatment of the renal insufficiency should be instituted but are of little avail. The anemia is most resistant to therapy of any kind.

It has been suggested that the sequence of events leading to the bone disease might be 1) decreased phosphorus excretion in the urine, 2) increased serum phosphorus level, 3) increased fecal phosphorus excretion,

4) formation of insoluble calcium phosphate in the gut and 5) decreased calcium absorption from the gut. Because of this suggestion it was hoped that the administration of aluminum hydroxide would interrupt this sequence by leading to the formation of insoluble aluminum phosphate in the gut. It was found that the administration of aluminum did result in an increased fecal phosphorus, a return of the serum phosphorus level to normal and a rise in the serum calcium level to normal but the net result *was markedly negative phosphorus and calcium balances and a worsening of the underlying bone disease.* After all calcium phosphate can not be deposited in bone if there is no phosphate!

It will be seen that there are three conditions which must not be confused. They are (a) primary hyperparathyroidism with osteitis fibrosa and kidney disease due to a parathyroid adenoma, (b) primary hyperparathyroidism with osteitis fibrosa and kidney disease due to idiopathic parathyroid hypertrophy, and (c) renal insufficiency with a compensatory hyperplasia of parathyroid tissue and osteitis fibrosa generalisata.

One case has come to the authors' attention [Downs and Scott (1941)] in which primary hyperparathyroidism and secondary hyperparathyroidism were present in the same individual. The sequence of events was apparently as follows: (a) primary hyperparathyroidism due to a parathyroid adenoma, (b) increasing renal insufficiency, (c) such a degree of renal insufficiency that more parathyroid hormone was needed because of the tendency to phosphate retention than was being produced by the adenoma, (d) resulting hyperphosphatemia, (e) hypocalcemia, and (f) hyperplasia of the remaining parathyroid glands.

This case teaches an important lesson. In a patient with primary hyperparathyroidism and marked kidney damage the surgeon should probably leave behind considerably more parathyroid tissue than he otherwise would. This usually means doing a subtotal removal of the parathyroid adenoma, otherwise the patient will probably develop severe postoperative hypocalcemia and tetany.

(2) With Tubular Dysfunction but Without Phosphate Retention

One also meets compensatory hyperparathyroidism in a specific form of renal tubular disease in which there is relatively little glomerular insufficiency. This is discussed in detail in Chapter 7, p. 227.

CHAPTER 4

MODE OF ACTION OF VITAMIN D* AND DIHYDROTACHYSTEROL (A T 10)†

The following discussion is taken almost verbatim from Albright, Burnett, Parson, Reifenstein, and Roos (1946). Many of these data originally came from Albright and Sulkowitch (1938) and Albright, Bloomberg, Drake, and Sulkowitch (1938).

I STUDIES OF ACTION OF VITAMIN D

It should be emphasized that, in order to unravel the action of vitamin D, it is necessary to study its effect on parathyroidless individuals, otherwise one runs into the danger of considering as primary sequelae of the action of vitamin D changes which are secondary to an alteration in activity of the parathyroid glands. There are seven points from these previous studies which the authors would like to emphasize.

(A) Point 1. Relation of Vitamin D to Fecal Calcium and Phosphorus Excretions

The starting-off point of any discussion of the action of vitamin D is the repeatedly demonstrated fact that its administration decreases the fecal calcium and phosphorus excretions. This was clearly shown by Bauer

* In this section no distinction is made between vitamin D₂ (activated ergosterol, calciferol, and viosterol) and vitamin D₃ (activated 7-dehydrocholesterol). All the metabolic studies reported were carried out with vitamin D₂. Vitamin D₂ is a pure crystalline substance prepared by ultraviolet irradiation of ergosterol; it has a potency per gamma of 40 U S P units of vitamin D or of 40 mg. of an International Standard Solution of irradiated ergosterol. It is potent by mouth. There is no vitamin D. Vitamin D (unspecified) is a general term for all compounds in this group.

† Dihydrotachysterol or A T 10 (antitetanisches Präparat Nr. 10) is a crystalline derivative of an ultraviolet irradiation product of ergosterol. It is available in oil containing 1.25 mg. per cc. Prior to June 1942 the same preparation was labelled 5 mg. per cc. because of the presence of then unrecognized inert materials. It is potent by mouth. A T 10 is distributed in the United States as Hytakerol by the Winthrop Chemical Company, New York, N. Y.

Fig. 59. Effect of Vitamin D on Nitrogen, Phosphorus, and Calcium Metabolisms in a Patient with Osteomalacia Secondary to Steatorrhea.

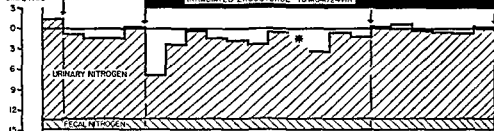
For explanation of construction of chart see Appendix, page 309.

Note low urinary calcium excretion throughout and markedly decreased fecal phosphorus and fecal calcium excretions upon administration of vitamin D in period 29. [From Albright, Burnett, Parson, Reifenstein, and Roos (1946), diagram constructed from data of Bauer, Marble, and Clafin (1932) with permission of the authors and the Journal of Clinical Investigation.]

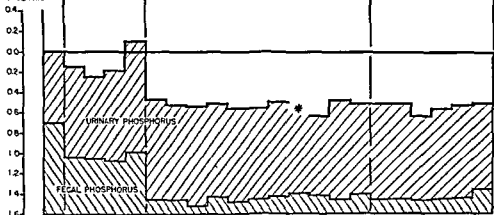
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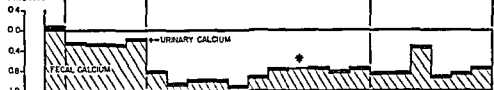
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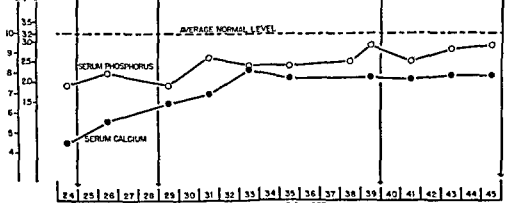
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GM/24 HR



MG/100 CC
CA P



* CATANEMA URINARY NITROGEN 44.70 GM/24 HR

* CALCIUM 2.25

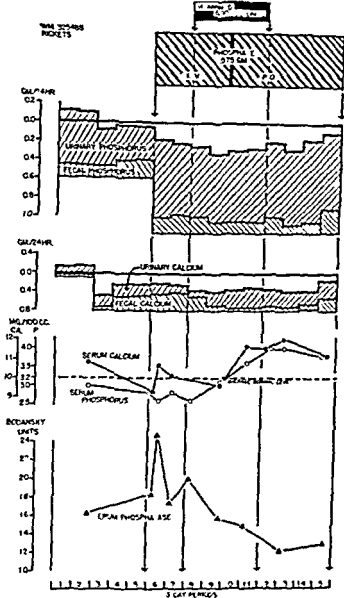


Fig. 60 Metabolic Data on Patient (W. M., M. G. H. 325188) with Vitamin D Resistant Rickets

For explanation of construction of chart see Appendix page 377

The chart is self-explanatory. The points discussed in the text are: the rise in fecal calcium and phosphorus excretions following an increase in calcium intake (see periods 3 through 5), the failure of the fecal phosphorus excretion to rise when phosphorus was administered intravenously (see periods 6 through 9) or by mouth (see periods 10 and 11), the fall in fecal calcium and phosphorus excretions following administration of vitamin D (see periods 8 through 11), the failure of intravenous phosphorus to elevate the serum phosphorus (see periods 6 and 7) and the rise in serum phosphorus without an increase in urinary phosphorus excretion following administration of vitamin D (see periods 8 to 11). [From Albright and Burnett, Parson, Reifenstein, and Roos (1946), recharted from Albright and Salkowitch 1935.]

Marble and Claflin (1932) in metabolic periods 29 through 45 (see Fig 59) and is also well demonstrated in Fig 60 in metabolic periods 8 to 10 in Fig 61 in metabolic periods 10 through 13 and in Fig 62 in metabolic periods 15 to 20. But this is not enough one would like to know whether the changes in calcium metabolism are due to changes in phosphorus metabolism or vice versa whether the decreased fecal excretions are due to increased absorptions from the gut or decreased re-excretions into the gut *et cetera*. It is necessary, therefore to explore these studies further.

(B) *Point 2 Relation of Dietary Calcium and Phosphorus to Fecal Calcium and Phosphorus Excretions*

An increase in calcium in the diet increases the calcium in the feces and this in turn increases the phosphorus in the feces on the other hand an increase of phosphorus in the diet has very little effect on the fecal phosphorus excretion or on the fecal calcium excretion. These facts were well brought out in studies on a patient with vitamin D resistant rickets (see Fig 60). When the calcium in the diet was increased (see metabolic periods 3 through 5) there was a definite increase in the fecal calcium and phosphorus excretions on the other hand when the phosphorus which had previously been given intravenously was administered by mouth in period 10, there was no increase in the fecal phosphorus excretion or in the very low fecal calcium excretion. Illustrative of the same point are the data of Gargill, Gilligan and Blumgart (1930) recharted in Fig 63 on a patient with osteomalacia. Note especially that the fecal phosphorus was not increased in periods 21 to 24 when the phosphorus intake was increased fivefold. It should be noted that these findings are merely confirmatory of previous findings by Nicolayson (1937) on rats.

As a corollary to points 1 and 2 it follows that vitamin D decreases the fecal phosphorus excretion through its effect on the fecal calcium excretion. This corollary was likewise arrived at by Nicolayson (1937) in his studies on rats.

(C) *Point 3 Relation of Vitamin D to Calcium Absorption from Gut (First Action of Vitamin D)*

The decreased fecal calcium excretion with vitamin D is the result of increased calcium absorption from the gut and not of decreased calcium excretion into the gut. For the studies to demonstrate this (see Fig 61) a patient with idiopathic hypoparathyroidism with a low serum calcium level was chosen so that calcium given intravenously would not immediately appear in the urine. In Fig 61 it will be noted that when 500 mg of added calcium daily were administered intravenously during metabolic periods 4 and 5, there was no appreciable change in fecal calcium excretion. Later on (period 8) when the same amount of calcium was given by mouth

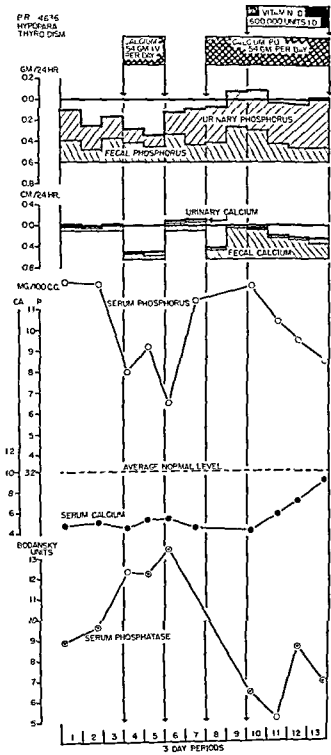


Fig. 61.

there was a marked increase in the fecal calcium excretion. Now when vitamin D was administered in period 10 the fecal calcium excretion showed a definite decrease. Thus, since it had already been shown that the giving of almost all of the calcium intravenously did not result in any increase in the amount of calcium appearing in the feces, this decrease of calcium in the feces with vitamin D could not have been due to decreased calcium re-excretion into the gut, one cannot decrease something which is non-existent. These findings are in agreement with those of Hannon, Lau Chiu Wang Chen, and Chou (1934), who found that calcium chloride administered intravenously was retained in osteomalacia which suggested that the high fecal calcium excretion in that condition is the result of lack of calcium absorption and not of increased re-excretion.

(D) *Point 4: Relation of Calcium Absorption Action of Vitamin D to Serum and Urinary Calcium Levels*

The increased calcium absorption from the gut partly explains—at least in patients with osteomalacia or rickets—the rise in serum calcium level and the increase in urinary calcium excretion which follow vitamin D therapy. The importance of the modifying factor partly will appear below. This rise in serum calcium level and urinary calcium excretion with vitamin D therapy is well shown in Fig. 60, metabolic periods 8 to 11.

(E) *Point 5: Relation of Vitamin D to Parathyroid Activity and Serum Phosphorus Level*

The rising serum phosphorus level following the administration of vitamin D is to be attributed only slightly, if at all, to the increased phosphorus absorption from the gut but mostly to decreased parathyroid activity resulting from the rise in serum calcium level. Thus to refer again to Fig. 60, if increased phosphorus absorption was the cause of the rising serum phosphorus level with vitamin D administration (see metabolic periods 8

Fig. 61 Metabolic Data on Patient (P. R. M. G. H. 4636) with Idiopathic Hypoparathyroidism

For explanation of construction of chart see Appendix, page 309

The figure is self-explanatory. The points emphasized in the text are: the failure of calcium administered intravenously to increase the urinary or fecal calcium excretions (see periods 4 and 5), the marked rise in fecal calcium and phosphorus excretions when the same amount of calcium was administered by mouth (see periods 8 through 10), the fall in fecal calcium and phosphorus excretions following administration of vitamin D (see periods 10 through 13), and the failure of the serum calcium to rise when calcium was given intravenously (see periods 4 and 5) as opposed to the definite rise in serum calcium following vitamin D (see periods 10 through 13) although the calcium balance was greater in periods 4 and 5 than in periods 10 through 13. [From Albright, Burnett, Parson, Riesenfeld and Roos (1936), recharted from Albright and Sulkowitch (1935).]

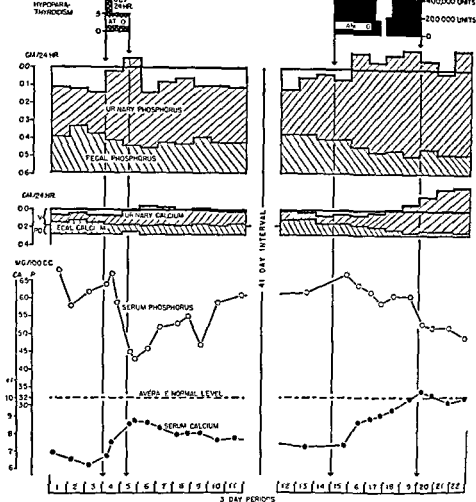


Fig 62 Metabolic Data on Patient (D B, M G H 8568) with Idiopathic Hypoparathyroidism

For explanation of construction of chart see Appendix, page 300

The chart is self-explanatory. Note that more than one half the calcium intake was given intravenously. Note the fact that the urinary excretions of calcium and phosphorus as the result of vitamin D administration (see periods 15 through 22) increased more than the fecal excretions decreased, thus leading to negative calcium and phosphorus balances, the fact that the sequelae following administration of dihydratachysterol (A T 10) were qualitatively the same as those following vitamin D but quantitatively different in that the ratio of the phosphorus-excretion-effect to the calcium absorption-effect was greater with dihydratachysterol than with vitamin D, and the fact that the serum phosphorus level fell more with dihydratachysterol for any degree of elevation of serum calcium than it did with vitamin D. Not commented upon but of interest was the failure of the serum calcium level to rise above normal following vitamin D therapy (period 20 to 22), although the serum phosphorus continued to fall and the serum calcium excretion increased at an accelerated rate [From Albright, Burnett, Parson, Reifenstein, and Roos (1946), recharted from Albright, Bloomberg, Drake, and Sulkowitch (1938)]

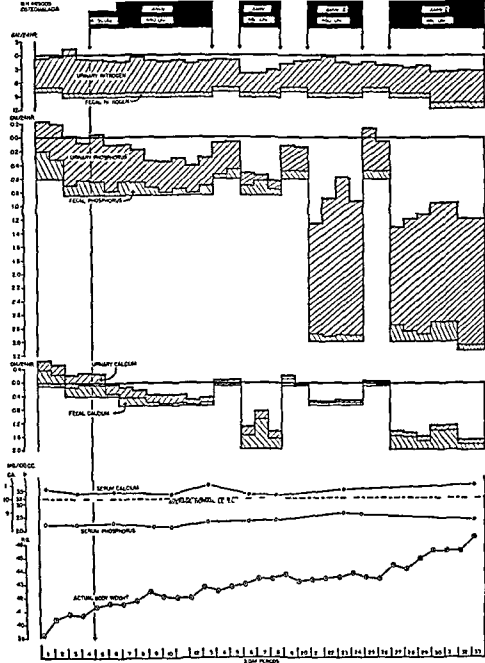


Fig 63 Metabolic Studies on Patient with Osteomalacia of Questionable Etiology—Possibly Idiopathic Hypercalcaemia

For explanation of construction of chart see Appendix, page 300

The points emphasized in the text are large amount of calcium in the urine in spite of severe osteomalacia, decrease in fecal calcium and phosphorus on administration of vitamin D (see periods 5 through 14), lack of effect of phosphorus intake on fecal phosphorus excretion (compare periods 22-25 with periods 26-27) and parallelism between fecal calcium excretion and fecal phosphorus excretion (compare periods 22-25 with periods 27-31) [From Albright, Burnett, Parson, Reifenstein, and Roos (1946), recharted from Gargill, Gilligan, and Blumgart (1930), with permission from the Archives of Internal Medicine] See also discussion on p 218

through 11) the serum phosphorus should have risen during periods 6 and 7 when a large amount of the phosphorus was given intravenously. Such was not the case in spite of the fact that the urinary phosphorus excretion during periods 6 and 7 did increase markedly. On the other hand when vitamin D was administered the serum phosphorus rose with no appreciable change in the urinary phosphorus excretion. Thus in metabolic period 6 with a serum phosphorus level of 2.7 mg/100 cc. the patient excreted 2465 mg. of phosphorus in the urine whereas in period 13 with a serum value of 4.0 mg/100 cc. he excreted 2376 mg. in the urine. This lack of increase in the urinary phosphorus excretion in the presence of a rising serum phosphorus level is most suggestive of a decrease in the activity of the parathyroid gland and in the authors' opinion is so to be interpreted. This point of view gains weight from the fact that when one administers vitamin D to parathyroidless individuals the serum phosphorus level does not rise (*vide infra*).

(F) *Point 6: Relation of Vitamin D to Phosphorus Excretion in Urine*
(*Second Action of Vitamin D*)

Whereas all the sequelae to the administration of vitamin D so far mentioned are attributable in the authors' opinion to the increased calcium absorption from the gut, there are other sequelae which make it necessary to hypothesize a second equally fundamental action of vitamin D, namely to cause an increased urinary phosphorus excretion. In the first place it was shown by Gyorgy (1930) that massive doses of vitamin D cause decalcification; it would be hard to explain decalcification if the only action of vitamin D were to increase calcium absorption. The second action of vitamin D is well brought out in Fig. 62 which shows studies on a patient with idiopathic hypoparathyroidism. It will be noted that during the administration of large doses of vitamin D (metabolic periods 15 through 19) the fecal calcium excretion fell, the serum calcium level rose and the urinary calcium excretion rose, all of which were to be expected, but the urinary calcium excretion rose more than the fecal calcium excretion fell so that the patient went into a strongly negative calcium balance! The explanation is to be seen in the phosphorus metabolic data. With vitamin D administration the urinary phosphorus excretion rose more than the fecal phosphorus excretion fell and the serum phosphorus level fell. It would seem that vitamin D in large doses has an effect on phosphorus metabolism similar to the parathyroid hormone and that as discussed elsewhere [Albright and Sulkowitch (1938)] this effect of vitamin D on phosphorus excretion in the urine is entirely separate from its action on calcium absorption from the gut. That the increased phosphorus excretion in the urine following vitamin D administration is not a sequel of the increased calcium absorption is shown in Fig. 61 where the intravenous ad-

ministration of calcium (periods 4 and 5) was followed by a decreased rather than an increased urinary phosphorus excretion

A second piece of evidence that the two actions of vitamin D are independent of each other lies in the studies of Albright, Bloomberg, Drake, and Sulkowitch (1938) from which they concluded that dihydrotachysterol (A 110) a substance very similar to vitamin D has the same two actions but in a different ratio one to the other, it was their conclusion that dihydrotachysterol has more phosphorus excretion-effect per unit of calcium absorption effect than vitamin D (see Fig 62 and 64). It should be noted in Fig 62 and 64 that the serum phosphorus level following administration of dihydrotachysterol was lower for any level of serum calcium than following the administration of vitamin D.

In patients with their parathyroids intact the second effect of vitamin D to increase the urinary excretion of phosphorus may be entirely masked by the first effect. Thus the sequence of events—increased calcium absorption rising serum calcium decreased parathyroid activity depressed urinary phosphorus excretion rising serum phosphorus level—results in the opposite effect on the phosphorus metabolism hence, whether the serum phosphorus goes down or up with vitamin D administration will depend on which effect of vitamin D predominates. Since one cannot decrease parathyroid activity in parathyroidless individuals the urinary phosphorus excretion must rise and the serum phosphorus level must fall with vitamin D administration in such individuals (see Fig 61, 62 and 64).

(G) *Point 7 Relation of Urinary Phosphorus Excretion Action of Vitamin D to Serum Calcium Level*

The rising serum calcium level following the administration of vitamin D to a normal or hypoparathyroid individual is to be attributed to the urinary phosphorus excretion effect and not to the calcium absorption effect of vitamin D. Fig 61 is most instructive as regards this point. When 510 mg of calcium daily were administered intravenously to the patient with idiopathic hypoparathyroidism (metabolic periods 4 and 5) there was a marked fall in the serum phosphorus level and in the urinary phosphorus excretion, but no rise in the serum calcium level, evidently calcium phosphate was formed and deposited somewhere possibly in the bones possibly in the reticulo-endothelial cells. Quite different were the sequelae to the administration of vitamin D (see periods 10 through 13). There instead of a fall in the urinary phosphorus excretion there was a rise, the serum phosphorus level fell as it did following administration of calcium intravenously, but the serum calcium level rose in spite of the fact that the positive calcium balance resulting from the decreased fecal calcium excretion was less than the positive balance resulting from the intravenously administered calcium. It is quite clear from these observations that to

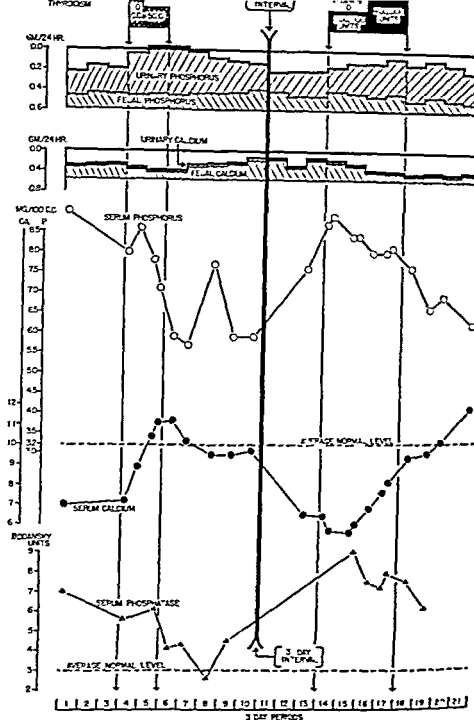


Fig 64 Metabolic Data on Patient (W.C., M.G.H. 14727) with Idiopathic Hypoparathyroidism Recharted from Albright, Bloomberg, Drake, and Sulkowitch (1929) to Contrast the Effect of Dihydroxycholesterol (A.T. 10) with That of Vitamin D. For construction of chart see Appendix, page 300.

Note: calcium phosphorus level for any given rise in serum calcium is lower than with vitamin D. [From Albright and Potts (1946)]

raise the serum calcium level in the hypoparathyroid individual, and the same is probably true of the normal, it is necessary that space be made as it were, by the removal of phosphate so that more calcium can be dissolved in the body fluids. In the patient with osteomalacia or rickets, on the

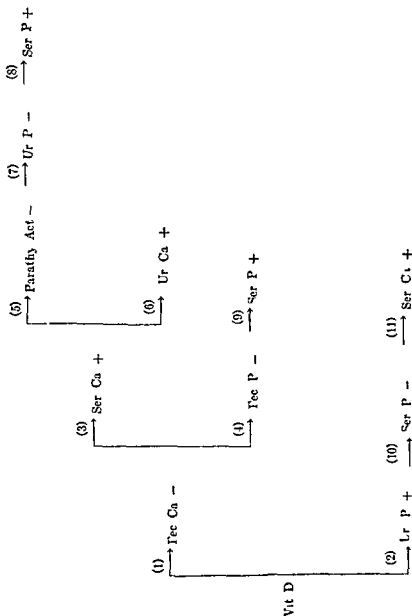


Fig. 65 Diagram to illustrate Metabolic Sequelae of Vitamin D Action
[From Albright Burnett Parson Reifenstein and Roos (1916)]

other hand, where the body fluids are depleted as regards calcium and phosphate ions, the increased absorption of calcium resulting from vitamin

It follows from the above discussion that the phosphorus-excretion-effect of dihydrotachysterol or of vitamin D and not the calcium absorption effect is the significant property of these substances in the treatment of hypoparathyroidism, the converse is true in the treatment of osteomalacia. Thus, dihydrotachysterol would seem to be the better agent in the treatment of hypoparathyroidism, and vitamin D the better agent in the treatment of osteomalacia.

II THE TWO ACTIONS OF VITAMIN D AND THEIR SEQUELAE

In Fig. 65 the two actions of vitamin D and the various sequelae of each action are summarized in diagrammatic form. It will be noted that whether the serum phosphorus rises (arrow 8) or falls (arrow 10) will depend on whether the first action of vitamin D (arrow 1) or the second action of vitamin D (arrow 2) predominates and that in parathyroidless individuals arrows 5, 7, and 8 drop out. A diagram for dihydrotachysterol would be the same except that arrows 2, 10, and 11 would be increased in size.

TABLE 2

Relative Effect of Vitamin D, Dihydrotachysterol, and Parathyroid Hormone on Intestinal Calcium Absorption and Urinary Phosphorus Excretion

	Calcium Absorption	Urinary Phosphorus Excretion
Vitamin D	++++	++
Dihydrotachysterol	++	+++
Parathyroid hormone	+	++++

This dual action of vitamin D, which has been proposed, is not out of harmony with the findings of Harrison and Harrison (1941) who studied factors influencing re-absorption of phosphorus from the kidney tubules. They showed that the parathyroid hormone decreases re-absorption and that vitamin D in rachitic animals only, increases re-absorption. It seems likely that the increased re-absorption with vitamin D is due to a secondary decreased parathyroid activity; the experiment should be repeated on parathyroidectomized animals in which case the present authors would predict a decrease in phosphate re-absorption in the tubules.

It would appear from the above discussion that dihydrotachysterol holds an intermediate position between vitamin D and the parathyroid hormone (see Table 2). In Fig. 112 p. 222 some data recharted from Albright, Sulkowitch, and Bloomberg (1939) bring into contrast the metabolic effects of vitamin D, dihydrotachysterol, and the parathyroid hormone.

The applicability of the findings presented in this Chapter to the mechanism of hypervitaminosis D and its treatment is discussed elsewhere (see p. 95).

CHAPTER 5

METABOLIC BONE DISEASE GENERAL CONSIDERATIONS

I OSTEOGENESIS

(A) *Types of Osteogenesis*

There are three types of bone formation (a) endochondral, (b) membranous, and (c) endosteal

The steps in the formation of bone from cartilage are (a) proliferation and hypertrophy of cartilage cells, (b) arrangement of more mature cells into rows, (c) calcification of intercellular cartilaginous substance between rows (so called zone of provisional calcification), (d) the breaking of blood vessels from below into the rows of lacunae containing the cartilage cells, (e) the laying down of bony matrix (osteoid) by osteoblasts on to the surfaces of the calcified cartilaginous trabeculae left after the blood vessels have broken into the lacunae, and (f) the deposition of a calcium phosphate carbonate salt into the osteoid

It will be noted that one trabecula is formed for every column of extracellular cartilaginous substance between the rows of cartilage cells these trabeculae, in the event that they are formed from the epiphyseal cartilage of a long bone, are all parallel to one another and run in the long axis of the bone They are designated "primary trabeculae" In the process of remodeling of the bone, most of the primary trabeculae are resorbed and replaced by larger "secondary trabeculae" which take any shape or direction which the internal dynamics of the bone requires It will be further noted that the primary trabeculae, when first formed before the osteoblasts have coated them with bone, consist merely of calcified cartilage They constitute at this stage a weak spot and it is here that epiphyses slip It follows that the purpose of the calcification of the zone of provisional calcification is to make the primary trabeculae, while still composed of cartilage alone as rigid as possible

The term "membranous bone" is usually reserved to designate that bone which is formed directly from specialized mesenchymal tissue in the embryo without there having been any preceding cartilaginous phase We will use this term, perhaps somewhat loosely, to include periosteal bone formation

By "endosteal bone formation" we refer to that appositional bone laid down in the cortex and trabeculae of bone as a part of the constant remodeling of bone which takes place during growth and after growth has ceased

In the final analysis it will be noted that all three of these types of bone formation are essentially the same, namely the laying down by osteoblasts

of an extracellular substance called osteoid, and the deposition into this osteoid of a calcium phosphate-carbonate salt. However, as will be seen elsewhere, certain hormones have a selective action on one of the three types of bone formation, certain others on another, *et cetera*. And so it perhaps will be useful to continue to speak of them as three different processes.

(B) *Definition of Bone*

It should be noted that bone is first a tissue and secondly a calcified (or phosphorized) tissue. In order to emphasize this point one might use as his definition of bone "any tissue containing bone matrix." This definition would allow then for two subclassifications, uncalcified bone and calcified bone. According to the above definition, rickets, as will be seen elsewhere (see p. 144), would be a disease characterized by too much bone. However to conform with popular usage, we will use the term 'bone' to indicate calcified bone matrix (see Table 3).

(C) *Remodeling of Bone*

In adult bone, and even more so in growing bone, there is a constant remodeling going on. There are places where bone is being re-orbed and others where bone is being laid down. Both of these processes go on at one and the same time. This can best be demonstrated in a condition where both processes are speeded up, namely osteitis fibrosa generalisata (see Fig. 66). One is fortunate in the study of bone in that both of these processes can be seen under the microscope: osteoblasts where bone is being formed and osteoclasts where bone is being destroyed. It is probable that anabolism and catabolism are more or less constant features of all tissues but with most tissues (e.g. muscle) one can say only that the tissue is increasing or decreasing without being able to conclude whether the process which leads to the imbalance is a disturbance of anabolism or of catabolism.

(D) *Physiology of Normal Bone*

For a discussion of the physiology of normal bone see p. 9.

II CLASSIFICATION OF METABOLIC BONE DISEASE IN ADULTS

In Table 3 a classification of metabolic bone disease in adults is given. It will be seen that the two main divisions are 'Too-Little-Calcified Bone' and 'Too-Much Calcified Bone'. Note that in this Table we refer only to calcified bone. Thus, osteomalacia (adult rickets), where bone matrix is laid down but not calcified, comes under 'Too Little-Calcified Bone'. The 'Too-Much Calcified Bone' is divided into two categories: (a) 'Bone-Resorption Too-Much'. Since



Fig. 66 Pictomicrograph of Bone Biopsy from a Patient with Hyperparathyroidism and Osteitis Fibrosa Generalisata.

Note that at least one half of the bone surfaces is covered with osteoclasts indicating bone destruction and about one half with osteoblasts indicating bone formation. Note narrow osteoid seams. obl = osteoblasts, ocl = osteoclasts, b = bone trabeculae, and ost = osteoid seam. [From Albright (1947a)]

TABUL 3

Metabolic Bone Diseases in Adults

-
- | | |
|----|---|
| I | Too Little Calcified Bone |
| A | Bone Formation Too Little |
| a) | Defect in Matrix Formation Osteoporosis |
| b) | Defect in Calcification of Matrix Osteomalacia |
| B | Bone Resorption Too Much |
| a) | Osteitis Fibrosa Generalisata |
| II | Too Much Calcified Bone |
| A | Bone Formation Too Great |
| a) | Increased Matrix Formation Elemental Phosphorus Poisoning Excessive Stress Healed Osteitis Fibrosa Generalisata and Healed Osteomalacia |
| B | Bone Resorption Too Little |
| a) | Osteopetrosis |
| b) | Hypoparathyroidism |
-

bone formation consists of two steps: the laying down of the matrix by the osteoblasts and the deposition of the calcium salts in this matrix. "Bone Formation Too Little" can be subdivided into "Osteoporosis", where the

of an extracellular substance called osteoid, and the deposition into this osteoid of a calcium phosphate-carbonate salt. However, as will be seen elsewhere, certain hormones have a selective action on one of the three types of bone formation, certain others on another, *et cetera*. And so it perhaps will be useful to continue to speak of them as three different processes.

(B) *Definition of Bone*

It should be noted that bone is first a tissue and secondly a calcified (or phosphorized) tissue. In order to emphasize this point one might use as his definition of bone 'any tissue containing bone matrix'. This definition would allow then for two subclassifications, uncalcified bone and calcified bone. According to the above definition, rickets, as will be seen elsewhere (see p. 144), would be a disease characterized by too much bone. However, to conform with popular usage we will use the term 'bone' to indicate calcified bone matrix (see Table 3).

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In adult bone, and even more so in growing bone, there is a constant remodeling going on. There are places where bone is being resorbed and others where bone is being laid down. Both of these processes go on at one and the same time. This can best be demonstrated in a condition where both processes are speeded up, namely osteitis fibrosa generalisata (see Fig. 66). One is fortunate in the study of bone in that both of these processes can be seen under the microscope, osteoblasts where bone is being formed, and osteoclasts where bone is being destroyed. It is probable that anabolism and catabolism are more or less constant features of all tissues, but with most tissues (*e.g.* muscle) one can say only that the tissue is increasing or decreasing without being able to conclude whether the process which leads to the imbalance is a disturbance of anabolism or of catabolism.

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'Too-Little-Calcified Bone' is divided into two categories: (a) 'Bone-Formation Too-Little', and (b) 'Bone-Resorption Too-Much'. Since



Fig 66 Photomicrograph of Bone Biopsy from a Patient with Hyperparathyroidism and Osteitis Fibrosa Generalisata

Note that about one half of the bone surfaces is covered with osteoclasts indicating bone destruction, and about one half with osteoblasts indicating bone formation. Note narrow osteoid seams. obl = osteoblasts, ocl = osteoclasts, b = bone trabeculae, and ost = osteoid seam. [From Albright (1947a)]

TABLE 3

Metabolic Bone Diseases in Adults

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| a) | Osteitis Fibrosa Generalisata |
| II | Too Much Calcified Bone |
| A | Bone Formation Too Great |
| a) | Increased Matrix Formation Elemental Phosphorus Poisoning
Excessive Stress Healed Osteitis Fibrosa Generalisata and Healed
Osteomalacia |
| B | Bone Resorption Too Little |
| a) | Osteopetrosis |
| b) | Hypoparathyroidism |
-

bone formation consists of two steps, the laying down of the matrix by the osteoblasts, and the deposition of the calcium salts in this matrix, "Bone-Formation-Too Little" can be subdivided into "Osteoporosis", where the

defect is in the laying down of the matrix, and "Osteomalacia", where the defect is in the calcification of the matrix. "Osteogenesis Imperfecta" is closely related to "Osteoporosis", it differs in that instead of a deficiency in the number of osteoblasts there is a deficiency in the amount of extra cellular substance made by them. In either case there results too little



Fig 67 Increased Epiphyseal Bone Formation Secondary to Elemental Phosphorus Administration

First x ray (A) was taken on 5-1-33 several weeks after stopping a short course of 'phosphorated oil'. Note dense band of increased density in radial metaphysis note furthermore that this band is removed a short distance from the epiphyseal cartilage. Second x ray (B) was taken on 8-4-33 at the end of a second course of elementary phosphorus. Note second dense band in juxtaposition to epiphyseal cartilage.

bone matrix. "Bone-Resorption Too-Much" is met with in hyperparathyroidism and in chronic acidosis and leads to 'Osteitis Fibrosa Generalisata'.

"Too-Much Calcified Bone" again can be divided into two categories (a) 'Bone Formation Too-Great', and (b) 'Bone Resorption Too-Little'. 'Bone Formation Too-Great' would result from increased matrix formation. There is no very good example in clinical medicine of a generalized over production of matrix compared to the situation in mice treated with estrogens where the skeleton becomes very dense presumably due to

stimulation of the osteoblasts [Gardner and Pfeiffer (1943)]. To be sure, an individual doing very heavy muscular work has a denser skeleton than the desk worker, but he can not be said to have too much bone. In a way "Healed Osteitis Fibrosa Generalisata" and "Healed Osteomalacia" are examples of "Too-Much-Calcified-Bone"; here, however, increased matrix formation occurred when there was too little calcified bone (see p 114).

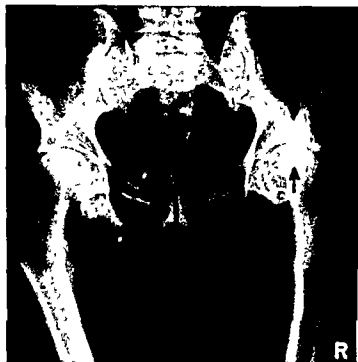


Fig 68. X-ray Film to Illustrate Hyperostosis at Point of Increased Stresses

Note increased bone density (arrows) in acetabulum on right side, where loss of cartilagenous cushion as result of degenerative arthritis has resulted in bone meeting bone

There are local conditions which serve as examples of increased matrix formation such as the increased bone formation at the growing epiphyseal lines in "Elemental Phosphorus Poisoning" (see Fig. 67), and the chonization of bone which occurs when bone is exposed to unusual stress. An example of the latter occurs in degenerative arthritis of the hip ("Morbus Coxae Senilis"), where because of the loss of the cartilagenous cushion bone meets bone (see Fig. 68). Since matrix is either calcified or not calcified and can not be super-calcified, there is no counterpart under the heading "Too-Much-Calcified-Bone" to "Osteomalacia" under the heading "Too-Little-Calcified-Bone". "Bone-Resorption-Too-Little" is well exemplified

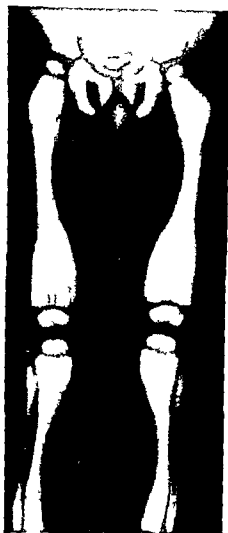


Fig 69 Osteopetrosis (Marble Bone Disease Albers Schonberg Disease) X-ray Film of Lower Extremities Showing Bone Lesions

Note the marked density of all bones. Note especially peculiar sclerotic appearance of metaphyseal bone. This appearance is due to two abnormalities both of which can be explained by decreased bone resorption — i.e. by decreased remodeling of bone. The first abnormality is a tendency for the metaphyseal bone to maintain the same circumference on cross section as was present when it was first made from epiphyseal cartilage. The second abnormality is the longitudinal striations which are due to the failure of the primary trabeculae to be resorbed and replaced by crisscrossed secondary trabeculae. (Patient B. L. MGH 96196)

by 'Osteopetrosis' (Marble Bones Albers Schonberg's Disease) where bone formed is apparently poorly if at all resorbed (see Fig 69). 'Hypo

parathyroidism is the second example. Here the resorption of calcite from the matrix according to our interpretation is decreased because of the increased phosphate level in the body fluids which is not quite offset by the lowered calcium level (see p. 17).



Fig. 10. X-ray Film Showing Heroination of Nucleus Pulposus Through Endplate of Vertebra (Schmorl's herniation).
[From Allright, Smith and Richardson (1911)]

III. PATHOLOGIC PHYSIOLOGY OF OSTEOPOROSIS, OSTEOMALACIA AND OSTEITIS FIBROSA GENERALISATA

It is important to make clear the differences between these three types of metabolic bone disease which are characterized by too little calcified bone.

In osteoporosis (see Fig. 39B, p. 82) the decrease of bone tissue is due

to the fact that the osteoblasts lay down too little bone matrix, that matrix which is laid down is normally calcified. Thus since osteoporosis is a disorder of tissue metabolism, not of calcium or phosphorus metabolism one is not surprised to find normal serum calcium and phosphorus levels. The



Fig 71 X ray Film Showing So Called 'Codfish Vertebra

Note that intervertebral disks have expanded into vertebrae converting them into biconcave disks of Fig 72 (From Albright, Smith and Richardson (1941))

serum alkaline phosphatase level the index to osteoblastic activity, is likewise normal not low as one might at first thought expect. A normal phosphatase level really means a relatively low level if one considers the fact that the skeletal mass being decreased is more subject to stresses and strain, the usual stimulus to osteoblasts.

In osteomalacia (see Fig 39C p 82) there is too little calcified bone due to the fact that there is a disorder of calcium or phosphorus metabolism of such a nature that the calcium phosphate-carbonate salt is not deposited in the newly formed osteoid. The bone tissue therefore is less resistant to



Fig 72 Codfish Vertebrae to Demonstrate What is Meant by a Codfish Vertebra

(A) X ray of four codfish vertebrae Note that the vertebrae are bi-concave discs (B) Drawing of one of the vertebrae shown in (A)



Fig 73 X ray Film Showing Crushed Vertebra
(From Albrigt, Smith and Richardson (1911))

stresses and strains and this results in an over production of osteoid by the osteoblasts. This in turn results in a high serum alkaline phosphatase level.

In *osteitis fibrosa generalisata* (see Fig. 39D, p. 82) there is a decrease in bone tissue as a whole because of increased bone resorption. This leads to decreased bone strength and this in turn to an increased activity on the part of the osteoblasts and hence to a high serum alkaline phosphatase level. The commonest cause of *osteitis fibrosa generalisata* is hyperparathyroidism which if present, is associated with low serum phosphorus and high serum calcium levels (see p. 72).

IV VERTEBRAL CHANGES

The vertebral changes here discussed are common to all bone conditions which lead to demineralized vertebrae e.g. osteoporosis, multiple myeloma, *et cetera*. The nucleus pulposus in the center of the intervertebral disc in the normal individual is kept from expanding in all directions by the intervertebral ligaments and the end plates of the vertebrae. In the presence of demineralized vertebrae a nucleus may break through the end plate and herniate into the body of the vertebra forming the so-called "Schmorl'sches Knotchen" (see Fig. 56 p. 118 and Fig. 70) or it may press the end plate into the shape of a concave disc (see Fig. 71). This leads to the so-called "cod fish vertebra" (sometimes erroneously called "fish tail vertebra") because it resembles the normal vertebra of the cod fish (see Fig. 72). Besides these changes the vertebrae may as a result of fracture be completely crushed, wedged, or telescoped at one end (see Fig. 73). An interesting example of cod fish vertebrae in a growing child with Cushing's syndrome and the changes after alleviation of the malady are shown in Fig. 84, 85, 86, and 87, p. 176-179.

CHAPTER 6

METABOLIC BONE DISEASE OSTEOPOROSIS

I CONDITIONS ASSOCIATED WITH OSTEOPOROSIS

In clinical medicine one encounters the following conditions associated with osteoporosis (Table 4) (1) disuse atrophy where the normal stimulus to osteoblastic activity is absent [Albright Burnett Cope and Parson (1941) Reifenstein and Albright (1944)] (2) malnutrition where the protein requirements are not fulfilled and the bone matrix like other tissues is depleted (3) scurvy where a normal constituent for formation of protoplasm ascorbic acid is deficient and the bone matrix shares in the depletion (4) the post menopausal state the commonest of all forms where the difficulty is a deficiency in estrogen to stimulate the osteoblasts (5) old age where the bone tissue like other tissues (cf hair skin muscles) atrophies (6) Cushing's syndrome where we believe an excess of the adrenal cortical Sugar or S hormone inhibits anabolism of protoplasm including bone matrix [Albright Parson and Bloomberg (1941) Albright (1942 1943)] (7) Adaptation Syndrome of Selye (1946) where we believe the pathological physiology is the same as in Cushing's syndrome (8) acromegaly where the cause may be the increase of pituitary hormone(s) or the secondary lack of gonadal hormones [Reifenstein Kinsell and Albright (1946)] and (9) idiopathic osteoporosis where the cause of the condition remains obscure. Frequently two or more factors combine in one individual thus after an orthopedic operation factors (1) and (7) probably both play a part (see p 185). It is to be noted that the above list does not include hyperthyroidism this will be discussed under malnutrition (see p 149). The same is true for the osteoporosis of patients with long standing poorly treated diabetes mellitus which will be discussed under the same heading. Furthermore the authors do not believe that calcium lack *per se* causes osteoporosis (for further discussion see p 148).

II CLINICAL ASPECTS OF OSTEOPOROSIS

Osteoporosis being a disease of tissue metabolism and not of calcium metabolism is associated with relatively normal serum calcium and phosphorus levels. To be sure in many cases of post menopausal osteoporosis the serum phosphorus values are slightly on the high side of normal. Thus the average serum phosphorus values of 42 cases reported by Reifenstein Kinsell and Albright (1946) was 3.75 mg per cent as compared with our average normal value of 3.21 mg per cent. (The difference is significant statistically.) Exceptions to the serum calcium level being normal occur

when young active children (see discussion on p 84) or persons with excessive bone formation compensatory to increased bone destruction as with Paget's disease (see discussion on p 200) are suddenly immobilized. The calcium in the urine in osteoporosis may be high, normal or low depending on the duration of the disease (see p 84 and 118). When hypercalcaemia is present it may be a cause of kidney stones. The serum alkaline phosphatase is normal, not low as one might expect (see discussion on p 142).

Osteoporosis in man, when due to a systemic cause, has a marked predilection for the vertebrae and pelvis and, to a lesser extent, the skull, and

TABLE 4
Causes of Osteoporosis

I	Defect in Osteoblasts
A	Loss of Stress and Strain
1)	Atrophy of Disuse
B	Lack of Estrogen
1)	Post Menopausal State
2)	Congenital Hypoestrogenism Ovarian Agenesis
C	Congenital Osteoblastic Defect
1)	Osteogenesis Imperfecta
II.	Defect in Matrix
A	Loss of Androgen
1)	Eunuchoidism
2)	? Senile Osteoporosis
B	Loss of Protein
1)	Malnutrition
2)	Hypovitaminosis C
3)	Cushing's Syndrome
4)	"Alarm Reaction"
III	Defect Unknown
A	Acromegaly
B	Idiopathic Osteoporosis

seldom involves the extremities. The lamina dura around the teeth, as seen by x ray, is characteristically intact, an important point in the differential diagnosis between this condition and osteitis fibrosa generalisata. This distribution of the malady, while uneven, has a rhyme and a reason to it, and does not rule out an hormonal disturbance, which characteristically should have a generalized distribution. For an analogous example Gardner (1936) found that estrogens cause dissolution of the pelvic bones of mice while stimulating bony proliferation in the femora.

A word in addition about the clinical aspects of post menopausal osteoporosis! A moderate degree of osteoporosis of the spine is almost physiological after the menopause, its degree increases as the time during which

the post menopausal state has existed increased. The condition may progress to collapse and deformity of multiple vertebrae. It is surprising how much deformity there can be without symptoms. The tendency is to exaggerate the seriousness of collapsed vertebrae and to immobilize a patient with this condition in a plaster cast for a long period of time. Such therapy by stopping stresses and strains only serves to increase the osteoporosis. Furthermore we feel that an artificial menopause as opposed to a physiological one leads to a more complete absence of gonadal hormones and hence to a more serious degree of osteoporosis.

(A) *Osteoporosis from Disuse*

Since the normal stimulus to the osteoblasts is stresses and strains any enforced immobilization (flaccid paralysis plaster cast *et cetera*) of all or part of the skeleton will lead to decreased osteoblastic activity, and hence *bone resorption continuing to osteoporosis of the parts of the skeleton immobilized*.

Detrick Whedon Shorr and Barr (1945-1946) put four normal young men to bed for five to six weeks in partial plaster casts and found calcium losses of 9 to 24 gm for the period of immobilization. These figures represent 1 to 2 per cent of the total body calcium of an average adult. The loss of skeleton in these immobilized adults was obviously nowhere nearly as great as in the young boy already mentioned (see p 85) who was immobilized essentially from the neck down because of a fractured hip. A point of some diagnostic importance is that atrophy of disuse rarely affects the skull thus a person lying quietly in bed uses his skull almost as much as in walking. This is in contrast to osteitis fibrosa generalisata where the skull is one of the first parts of the skeleton to show involvement. Furthermore the immobilized patient must eat and in so doing uses his jaws so that the lamina dura remains intact (see Fig 42 p 87).

Atrophy of disuse as mentioned above is probably a factor in the osteoporosis of old age (see p 162) and in the osteoporosis associated with the Adaptation Syndrome of Selye (see p 182). In rats osteoporosis of disuse has been produced in the bones of limbs paralyzed by brachial nerve section by Armstrong Knowlton and Gouze (1915). Treatment of the animals with estrogen reduced the atrophy of bone. In man the osteoporosis associated with disuse and the Adaptation Syndrome following orthopedic operations also responds to estrogen therapy (see Fig 95 p 191) in the same way as does the osteoporosis of the post menopausal state (see p 159).

Atrophy of disuse may complicate other forms of osteoporosis by initiating a vicious cycle for example a patient with post menopausal osteo-

porosis fractures a vertebra, is forced to immobilize her spine acquires more osteoporosis develops more fractures *et cetera*. The orthopedic surgeon sometimes unwittingly abets this vicious cycle by over enthusiastic immobilization.

Special attention should be called to the acute form of atrophy of disc. Since in osteoporosis bone formation decreases and bone resorption continues unabated hypercalcuria occurs and may lead to the same kidney complications as are found in hyperparathyroidism in which the hypercalcuria results from the hypercalcemia. In osteoporosis the degree of hypercalcuria—the diet being constant—depends on the discrepancy between bone destruction and bone formation. If osteoporosis develops gradually this discrepancy is at no time great and hypercalcuria is never marked. If on the other hand bone formation suddenly stops in a non-osteoporotic skeleton or in a skeleton in which the turnover of bone is greater than normal there is marked hypercalcuria. Two common causes for sudden cessation of bone formation are immobilization of the skeleton in a cast or freeing of skeleton of muscle pull as a consequence of poliomyelitis. We have cited elsewhere two case histories which illustrate these points (1) that of an active 14 year old boy who fractured his leg and had a large part of his skeleton immobilized in a cast (see p. 83) and (2) that of a 64 year old woman with extensive Paget's disease who also fractured a leg and had a considerable part of her diseased skeleton immobilized in a cast (see p. 293). So great was the resulting decrease in bone formation in both patients that not only hypercalcuria but also hypercalcemia occurred. The cause of the latter was presumably an inability of the kidney to excrete the calcium as rapidly as it came from the skeleton. Just why the high serum calcium level in the presence of a normal phosphorus level did not make the condition self limited by stopping bone resorption is not clear.

(B) Osteoporosis from Malnutrition

The part played by diet in osteoporosis is still not established. Diet of course has everything to do with osteomalacia but that is an entirely different disease. There are at least three ways in which diet might be thought to play a part. Some investigators apparently believe that the increased availability of calcium and phosphorus in the system as a result of a diet rich in these substances is a stimulus to osteoblastic activity. As far as we are aware there is no evidence to support this point of view. If the amount of calcium and phosphorus in the diet has any effect on the causation of osteoporosis it seems unlikely that it is by such a mechanism. A second possibility is that an increased availability of calcium and phos-

phorus in the system as a result of increases in the diet would decrease the amount of resorption of bone. If such were the case any primary hypofunction of the osteoblasts would be partially offset by the decreased resorption and the patient would be benefited. Such a hypothesis would explain the apparently beneficial effect obtained by Bauer and Marble (1932) and by Adams Boothly and Snell (1936) in the treatment of patients with osteoporosis with diets high in calcium and phosphorus and large amounts of vitamin D. We favor the second possibility it is in keeping with the concept which has been frequently emphasized from our clinic that a diet high in calcium and phosphorus prevents the decalcification due to hyperparathyroidism (see p 21 and 67). Finally as a third possibility a diet inadequate in protein might lead to a negative nitrogen balance, and this in turn might make it impossible for the osteoblasts to lay down the necessary organic matrix which is the first step in the formation of bone. We believe that some of the osteopathies which have been attributed to a lack of calcium and phosphorus in the diet are really due to protein starvation.

Diet to be of any value must be assimilated hence it is highly probable that factors affecting the gastrointestinal tract will play a part. Thus Meulengracht (1939) emphasized the importance of achylia gastrica as a contributing factor. Furthermore by removing the stomach osteoporosis can be produced in a dog [Bussaburger Freeman and Ivy (1938)] which also suggests a relationship between the gastric mucosa and bone formation.

There is some evidence which will be discussed under "Idiopathic Osteoporosis" (see p 197) that the height of the serum protein level may be a factor in bone formation and hence in osteoporosis.

The part played by thyrotoxicosis in the etiology of osteoporosis is also not certain (see p 150). Aub Bauer Heath and Ropes (1929) found that there are increased excretions of calcium in the urine and feces in thyrotoxicosis and decreased excretions in myxedema. Williams and Morgan (1940) presented some evidence that long standing thyrotoxicosis leads to increased radiability of the skeleton. However five of the seven patients mentioned by these authors had passed the menopause so that the cause of the osteoporosis may have been the post menopausal state. Furthermore as thyrotoxicosis leads to increased requirements of protein vitamins *et cetera*, a deficiency in protein vitamin C or some other substance may have been a contributing factor. That a depletion of protein may play a role is suggested by the observation that the administration of testosterone propionate in thyrotoxicosis not only leads to a strongly positive nitrogen balance but also to a marked lowering of the urinary calcium excretion [Kinsell, Hertz and Reifenstein (1944)].

Metabolic Study No 3

Case No 10 Post-Menopausal Osteoporosis, Artificial Menopause, Estradiol Benzoate Therapy

F F (M G II 156453), a 42 year old woman, had a bilateral oöphorectomy at the age of 41 for endometriosis, following the operation she had "nocturnal seizures", the exact nature of which was not determined. During the following year there was a gradual onset of back pain with increasing dorsal kyphosis and a loss of energy. On admission one year after operation, the patient was in good physical condition except for the deformities of her spine, her blood pressure was 130/80. X rays revealed typical cod fish deformity of many of the dorsal and lumbar vertebrae, a collapse of some vertebrae, and anterior wedging of others. Laboratory studies: serum calcium 10.5 mg per 100 cc, serum phosphorus 4.2 mg per 100 cc, serum alkaline phosphatase 3.6 Bodansky units, serum total protein 7.3 gm per 100 cc, normal glucose tolerance test, some hypoglycemia unresponsive in an insulin tolerance test, basal metabolic rate of minus 6, follicle stimulating hormone test positive for 25 mouse units per 100 cc, and 17 ketosteroid excretion of 4.3 mg per 24 hours. This case was mentioned in previous communications [Albright, Bloomberg and Smith (1940) *Case 1*, Albright, Smith, and Richardson (1941), *Case 37*, Fraser, Forbes, Albright, Sulkowitch, and Reifstein (1941) *Case 82*, and Reifstein and Albright (1947) *Case 1*].

The metabolic data of Case No 10 are shown in Fig 74. The first part of the study, conducted in five day periods, consisted of (1) three control periods, (2) five periods with estradiol benzoate 1.66 mg intramuscularly every three days, (3) 23 days with the same therapy at home, (4) two periods with the same therapy, (5) two periods with progesterone 10 mg intramuscularly daily in addition to the estradiol, and (6) 12 periods after the cessation of both medications. The patient was then discharged on estrogen therapy which was given continuously in varied dosage during the next three years, during this interval she was brought back to the metabolic ward for study (one to three five day periods) on three occasions.

The data (see Fig 74) are self explanatory. Attention should be called to (1) nitrogen, phosphorus, and calcium equilibria during the control periods (1-3), (2) the high serum phosphorus level which tended to fall under estrogen therapy (less marked in this case than in others (see p 155)), (3) the slight improvement in nitrogen balance under estrogen therapy, (4) the striking and growing decrease in calcium excretion, both fecal and urinary, with estrogen treatment and the gradual return (40 days) in the calcium excretion to pre-treatment levels following cessation of estrogen therapy, (5) the decrease with estrogen treatment in the phosphorus excretion almost entirely confined to the urinary component and reasonably proportional to the changes in the calcium and nitrogen metabolisms (see "Theoretical Nitrogen Balance"), (6) the failure of the serum phosphatase level, the index of osteoblastic activity, to rise under estrogen therapy, (7) the increase in nitrogen but not in calcium and phosphorus excretions in periods 11 and 12 with progesterone therapy, and (8) the tendency to retain extracellular fluids with estradiol therapy as suggested by the increase in the actual weight above the theoretical weight. The apparent discrepancy in the effect of estrogen on the calcium and phosphorus balances during periods 26 and 27 is probably to be explained by erroneously high fecal excretions resulting

We have observed osteoporosis in several cases of long standing, poorly treated diabetes mellitus. Here again, as in thyrotoxicosis, the prolonged use of protein for energy may result in a deficiency in some constituent of protoplasm which is needed for bone matrix formation.

(C) *Osteoporosis and Hypovitaminosis C*

It has been recognized for centuries that there are characteristic skeletal lesions in scurvy. In children the more common evidences of these lesions are the irregular broadened epiphyseal line, the lateral spurs and occasional dislocation of the entire epiphysis, the decreased calcification behind the epiphyseal line, the thin diaphyseal cortex and the rarified shaft [(McIntosh (1937))]. There is no doubt that normal calcification of bones and teeth is dependent upon adequate vitamin C (ascorbic acid) without which the osteoblasts do not function normally [Salter and Aub (1931)]. The osteoblastic activity as measured by the serum alkaline phosphatase level is markedly decreased in scurvy in children [Shwachman and Gould (1942)]. The studies of Wolbach (1937) have established that ascorbic acid is necessary for the formation of the collagenous material of all fibrous tissue structures, the matrices of bone, dentin, and cartilage, and all non-epithelial cement substance including that of the vascular endothelium.

It follows, therefore, that ascorbic acid deficiency leads to decreased bone matrix formation and in turn to osteoporosis. Since frank scurvy is relatively uncommon, ascorbic acid deficiency is usually not considered in the etiology of osteoporosis. However, as indicated above, deficiency in this vitamin may be an important contributing factor in cases of osteoporosis associated with malnutrition, hyperthyroidism, *et cetera*.

(D) *Osteoporosis Associated with the Post Menopausal State*

Post menopausal osteoporosis, although frequently overlooked in treatises on bone disease, is the commonest of all forms of osteoporosis, indeed, it is the commonest of all systemic osteopathies [Albright, Bloomberg and Smith (1940), Albright, Smith, and Richardson (1941)].

(1) Effect of Gonadal Hormones on the Skeleton

The effect of gonadal hormones of the skeleton of animals has been extensively studied and summarized by Gardner and Pfeiffer (1943). It appears that estrogen stimulates endostial bone formation in pigeons and mice, and that testosterone enhances this action in pigeons but inhibits it in mice. Our own studies in the human which follow (Metabolic Studies No. 3, 4, and 5) are in agreement with the findings in pigeons.

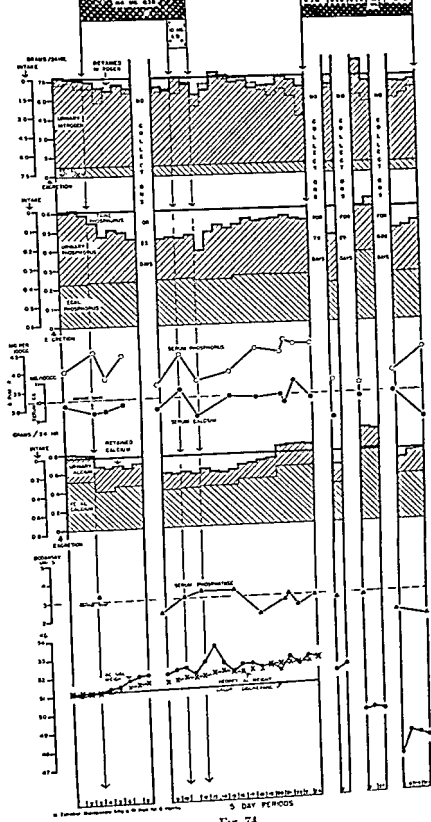
Metabolic Study No 3

Case No 10 Post Menopausal Osteoporosis, Artificial Menopause, Estradiol Benzoate Therapy

F. F. (M. G. H. 156453), a 42 year old woman, had a bilateral oöphorectomy at the age of 41 for endometriosis, following the operation she had "nocturnal seizures", the exact nature of which was not determined. During the following year there was a gradual onset of back pain with increasing dorsal kyphosis and a loss of energy. On admission one year after operation, the patient was in good physical condition except for the deformities of her spine, her blood pressure was 130/80. X rays revealed typical cod fish deformity of many of the dorsal and lumbar vertebrae, a collapse of some vertebrae, and anterior wedging of others. Laboratory studies: serum calcium 10.5 mg per 100 cc, serum phosphorus 4.2 mg per 100 cc, serum alkaline phosphatase 3.6 Bodansky units, serum total protein 7.3 gm per 100 cc, normal glucose tolerance test, some hypoglycemia unresponsive to an insulin tolerance test, basal metabolic rate of minus 6, follicle stimulating hormone test positive for 25 mouse units per 100 cc, and 17 ketosteroid excretion of 4.3 mg per 24 hours. This case was mentioned in previous communications [Albright, Bloomberg, and Smith (1940) *Case 1*, Albright, Smith, and Richardson (1941), *Case 37*, Fraser, Forbes, Albright, Sulikowitch, and Reifenshtein (1941) *Case 82*, and Reifenshtein and Albright (1947) *Case 1*].

The metabolic data of Case No. 10 are shown in Fig. 74. The first part of the study, conducted in five-day periods, consisted of (1) three control periods, (2) five periods with estradiol benzoate 1.66 mg intramuscularly every three days, (3) 23 days with the same therapy at home, (4) two periods with the same therapy, (5) two periods with progesterone 10 mg intramuscularly daily in addition to the estradiol, and (6) 12 periods after the cessation of both medications. The patient was then discharged on estrogen therapy which was given continuously in varied dosage during the next three years, during this interval she was brought back to the metabolic ward for study (one to three five day periods) on three occasions.

The data (see Fig. 74) are self explanatory. Attention should be called to (1) nitrogen, phosphorus, and calcium equilibria during the control periods (1-3), (2) the high serum phosphorus level which tended to fall under estrogen therapy (less marked in this case than in others (see p. 155)), (3) the slight improvement in nitrogen balance under estrogen therapy, (4) the striking and growing decrease in calcium excretion, both fecal and urinary, with estrogen treatment and the gradual return (40 days) in the calcium excretion to pre-treatment levels following cessation of estrogen therapy, (5) the decrease with estrogen treatment in the phosphorus excretion almost entirely confined to the urinary component and reasonably proportional to the changes in the calcium and nitrogen metabolisms (see "Theoretical Nitrogen Balance"), (6) the failure of the serum phosphatase level, the index of osteoblastic activity, to rise under estrogen therapy, (7) the increase in nitrogen but not in calcium and phosphorus excretions in periods 11 and 12 with progesterone therapy, and (8) the tendency to retain extracellular fluids with estradiol therapy as suggested by the increase in the actual weight above the theoretical weight. The apparent discrepancy in the effect of estrogen on the calcium and phosphorus balances during periods 26 and 27 is probably to be explained by erroneously high fecal excretions resulting



from too short a period of observation [see Reifenstein, Albright and Wells (1915)]

Metabolic Study No 4

Case No 11: Post-Menopausal Osteoporosis, Artificial Menopause, Methyl Testosterone, Estradiol Benzoate and Pregnenolone Therapy

R W (M G H 319940), a 56 year old woman had a cholecystectomy at 26, and thyroidectomy for thyrotoxicosis at 46. At 48 an artificial menopause was induced with radium for metropathia hemorrhagica. Three years before admission the patient strained her back opening a heavy window and thereafter had several episodes of sharp pain in the back when lifting. Physical examination showed a nervous woman with a tremor of her head and considerable deformity of her back. Her blood pressure was 115/75. X ray examination revealed extensive osteoporosis with multiple fractured vertebrae, the bones of the skull were approximately normal in density. Laboratory studies no abnormalities of the urine, stools, or blood cells, urine calcium 2 to 4 plus by the Sulkowitch test, serum calcium 10.6 mg per 100 cc, serum phosphorus 3.1 mg per 100 cc, serum alkaline phosphatase 3.7 Bodansky units, serum chloride 93.2 m eq per liter, serum carbon dioxide combining power 28.1 m eq per liter, serum non protein nitrogen 26 mg per 100 cc, and serum total protein 7.8 gm per 100 cc with an albumin/globulin ratio of 1.7. Electrocardiographic tracing was normal, follicle stimulating hormone excretion in the urine was high (consistent with the menopause). This case has been mentioned in previous communications [Reifenstein, Albright, Parson, and Bloomberg (1942) and Reifenstein and Albright (1947) Case 4].

Fig 74 Metabolic Study on Effect of Estradiol Benzoate on a Patient (F F M G H 156153) with Post Menopausal Osteoporosis Case No 10

For explanation of construction of chart see Appendix page 309

The dotted line in the nitrogen metabolism data represents the "theoretic nitrogen balance". The fecal nitrogen was estimated as 10 per cent of the intake. The fecal calcium and phosphorus values as charted are averages of 1, 2, 3, or 4 five day periods as follows: 1 through 3, 4 through 5, 6 through 8, 9 through 10, 11 through 12, 13 through 16, 17 through 20, 21 through 23, 24 through 27, 28 through 30, the individual values are given in Table 1 of the paper by Reifenstein and Albright (1947).

Note especially the initiation of a positive calcium balance on the administration of estradiol benzoate, the return to a negative calcium balance 9 periods (45 days) after cessation of therapy, that both urinary and fecal calcium excretions were affected, that there was a slight tendency to a positive nitrogen balance with estradiol benzoate therapy, that the phosphorus balance followed the nitrogen and calcium balances, that the increase in the phosphorus balance with estradiol benzoate therapy was the result of a decreased urinary phosphorus excretion, that the serum phosphorus values which tended to be high were on the whole lower during estradiol benzoate therapy, and finally, that periods 26 and 27 were out of line with respect to the calcium and phosphorus balances probably due to erroneously high fecal values resulting from too short a metabolic study. The added medication in periods 11 and 12 was progesterone, 10 mg daily by injection. [From Reifenstein and Albright (1947), and (Albright (1947a), recharted from Albright, Bloomberg and Smith (1940)].

The metabolic data of Case No. 11 are given in Fig. 75. The study, conducted in six-day periods, consisted of, (1) four control periods, (2) four periods on methyl testosterone, 40 mg. by mouth daily, (3) five periods in which 1.66 mg. of estradiol benzoate daily by injection were added to the methyl testosterone therapy, (4) five periods back on the methyl testosterone therapy alone, (5) four more control periods off medication, (6) three periods on pregnenolone, 30 mg. intramuscularly daily, (7) four more control periods off medication, (8) five periods back on methyl testosterone, 40 mg. by mouth daily with an increase in the nitrogen and phosphorus intakes during the last three of these, and (9) one final period where the methyl testosterone therapy was increased to 100 mg. by mouth daily. The urinary determinations were made on three-day periods throughout.

Fig. 75 is self explanatory. To be noted are (1) the decrease in the nitrogen, phosphorus, and calcium excretions with methyl testosterone therapy and the rebound of nitrogen and phosphorus excretions on cessation of therapy, (2) the fact that the fecal as well as the urinary excretions of both calcium and phosphorus were reduced under methyl testosterone therapy, (3) the fact that there was not an immediate rebound of the calcium excretion following cessation of methyl testosterone therapy, (4) the further improvement in the calcium balance but not in the nitrogen balance when estradiol benzoate therapy was added to the methyl testosterone therapy (periods 9-13), (5) the fall in serum phosphorus level with methyl testosterone and especially with estradiol benzoate therapy, (6) the definite tendency of the serum calcium level to parallel the serum phosphorus level, and (7) the failure of the serum phosphatase level to show a significant change. The effect of the pregnenolone therapy is inconclusive, it did not significantly affect the very low 17-ketosteroid excretion. No explanation is forthcoming in periods 29 and 30 for the low fecal calcium excretions not associated with low nitrogen and phosphorus excretions, as a result the data during periods 30 through 36 are difficult to interpret. The actual and theoretical weight curves suggest that there was retention of extracellular fluid with methyl testosterone therapy which was augmented when estradiol benzoate therapy was added. Pregnenolone therapy had a minimal effect on extracellular fluid retention.

Metabolic Study No. 5

Case No. 12: Post-Menopausal Osteoporosis, Artificial Menopause, Paget's Disease, Diethylstilbestrol and Progesterone Therapy

S. B. (M. G. H. 430664), a 58-year-old woman, had at the age of 28 a bilateral oophorectomy with a hysterectomy for pelvic lacerations following childbirth. For some years she had occasional hot flashes and attacks of palpitation and nervousness. At the age of 50 she began to notice weakness and gradual onset of skeletal deformities involving the skull, shoulder girdle, lower ribs, pelvis and bones of the legs. At 51 she had acute tonsillitis, and then a tonsillectomy. At 57 she had pneumonia, and after three weeks in bed increased weakness and pain in her tibiae. About this time she used braces of her legs because of difficulty in walking. Shortly afterward she developed low back pain on weight bearing.

On admission, the patient was undernourished and deformed with atrophic skin and muscles, dorsal kyphosis and right cervical dorsal scoliosis, enlarged parietal bosses, bowing of the femora and tibiae, and collapse of the lumbar spine so that the ribs touched the wings of the ilia. The chest was distorted, veins of the neck were distended, cor pulmonale was present, blood pressure was 126/80.

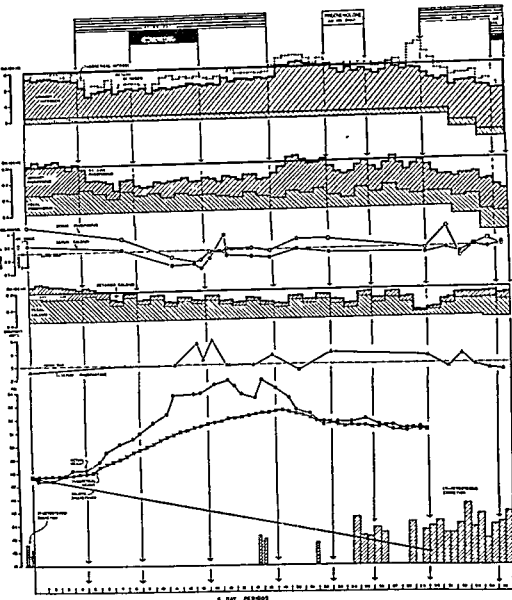


Fig 75 Metabolic Study on Effect of Methyl Testosterone Alone and in Combination with Estradiol Benzoate, and of Pregnenolone on a Patient (R W, M G II 319940) with Post Menopausal Osteoporosis, Case No. 11

For explanation of construction of chart see Appendix, page 309

Note the decrease in the nitrogen, phosphorus, and calcium excretions with methyl testosterone therapy, the immediate rebound of the nitrogen and phosphorus but not of the calcium excretions on cessation of therapy, the decrease in both the fecal and the urinary calcium and phosphorus excretions with methyl testosterone therapy, the further improvement in the calcium but not in the nitrogen balance when estradiol benzoate therapy was added to the methyl testosterone therapy, the fall in the serum phosphorus and calcium levels with both forms of therapy, the lack of significant change in the serum phosphatase level, the unexplained retention of calcium in periods 29 and 30, and the lack of significant effect from pregnenolone therapy [From Reifenstein and Albright (1947)]

X rays of the skull, shoulder girdle, lower ribs, pelvis, femora, tibiae, and entire thoracic and lumbar spine except for the upper three dorsal vertebrae showed Paget's disease, in addition there was marked generalized decreased density of bones and typical cod fish deformity of many vertebrae. There was pulmonary fibrosis, cardiac enlargement and displacement, and tortuosity of the aorta. Laboratory studies: serum calcium 10.5 mg per 100 cc, serum phosphorus 4.2 mg per 100 cc, serum alkaline phosphatase 34.3 Bodansky units, serum total protein 7.3 gm per 100 cc, serum non protein nitrogen 31 mg per 100 cc, serum sodium 140.0 m eq per liter, serum potassium 4.7 m eq per liter, serum chloride 101 m eq per liter, serum carbon dioxide content 34.2 m eq per liter, follicle stimulating hormone test positive for 192 mouse units per 24 hours and 17 keto steroid excretion 2.6 mg per 24 hours. The venous pressure was 65 mm of water, the vital capacity was 1200 cc. This case has been mentioned in a previous communication [Reifenstein and Albright (1947) Case 2].

The metabolic data of Case No. 12 are given in Fig. 76. The study conducted in six day periods, consisted of (1) three control periods, (2) five periods on 1 mg of diethylstilbestrol by mouth daily, (3) seven periods on 15 mg of diethylstilbestrol by mouth daily with an increase in diet in the last three of these, (4) six periods with the same dosage of diethylstilbestrol in which progesterone 1 cc injection was given in addition (25 mg daily for the first four of these periods and 100 mg daily for the last two), and (5) three periods on 15 mg of diethylstilbestrol daily alone.

This patient was selected for the study not only because she had marked osteoporosis from an artificial menopause 30 years before, but because she had in addition, Paget's disease. The primary pathologic process of the Paget's disease, bone destruction (see p. 285), was not being responded to with the usual amount of increased bone formation because of the menopause [Reifenstein and Albright (1944)]. Therefore, it was thought that any action of estrogen to stimulate bone formation would be magnified in this patient.

Fig. 76 is self explanatory. To be noted are (1) the markedly negative calcium and phosphorus balances during the control periods, (2) the marked improvement of these balances with 1 mg of diethylstilbestrol daily, (3) the further improvement with 15 mg of diethylstilbestrol daily, (4) the lack of effect of progesterone on the calcium and phosphorus balances, (5) the high serum phosphorus before treatment, (6) the tendency of the serum phosphorus to fall during treatment, (7) the failure of the serum phosphatase to rise with improvement of the

Fig. 76 Metabolic Study on Effect of Diethylstilbestrol Alone and in Combination with Progesterone on a Patient (S. B., M. G. H. 430661) with Post Menopausal Osteoporosis and Paget's Disease, Case No. 12.

For explanation of construction of chart see Appendix, page 309.

Note the markedly negative calcium and phosphorus balances in the control periods, the marked improvement in these balances with diethylstilbestrol therapy which increased as the dosage was raised, the lack of effect of progesterone therapy, the high serum phosphorus level before treatment and its fall during therapy, the failure of the serum phosphatase level to rise with improvement of the calcium balance, the fall in follicle stimulating hormone excretion with diethylstilbestrol therapy, the tendency to a rise in the 17 ketosteroid excretion and in the follicle stimulating hormone excretion with progesterone therapy, and the lack of effect of therapy on the 11 oxysteroid excretion level. [From Reifenstein and Albright (1947)]

calcium balance (8) the tendency of the 17 ketosteroid excretion to rise with progesterone (9) the failure of the 11-oxy steroid excretion* to fluctuate outside of the normal range with therapy (10) the striking fall in the urinary follicle stimulating hormone (FSH) excretion with diethylstilbestrol therapy and (11) the subsequent rise in the FSH excretion when progesterone therapy was superimposed on the diethylstilbestrol therapy. The increase in the positive nitrogen balance and the increase in weight during periods 22 to 24 after the omission of progesterone may be indications that progesterone was acting unfavorably on the nitrogen balance [Abels and Dobriner (1941)]. Not explained is the rise in the FSH excretion in periods 23 and 24.

On the basis of these three studies and of two others on patients with postmenopausal osteoporosis and of one on a patient with senile osteoporosis (see p. 162) the following conclusions can be made [Reifenstein and Albright (1947)]:

1 Estrogens in the two forms used (estradiol benzoate and diethylstilbestrol) decreased the calcium and phosphorus excretions in the types of osteoporosis studied. Additional observations on estrogen therapy are the following:

- a The fecal as well as the urinary calcium and phosphorus excretions were decreased in most instances.
- b The effects were usually manifest within 6 days, did not reach maximum until after 30 days, and persisted for 30-60 days after cessation of therapy.
- c The synthetic estrogen diethylstilbestrol appeared to be as effective as the naturally occurring estrogen, estradiol.
- d The range of dosages employed was for estradiol benzoate 1.66 mg every three days to 3.32 mg daily intramuscularly, and for diethylstilbestrol 1 to 15 mg daily by mouth. There was no convincing evidence that the larger doses of estradiol benzoate were more effective than the smaller; in one instance 3.32 mg seemed less effective than 1.66 mg every third day. In the one case studied, 15 mg of diethylstilbestrol daily was probably more effective than 1 mg daily.
- e The serum phosphorus levels, which tend to be high in the postmenopausal group, fell in almost all instances.
- f The serum alkaline phosphatase levels, contrary to expectations, did not rise.
- g The urinary nitrogen excretion showed a poorly sustained decrease.

* These observations were carried out by Dr. Nathan B. Talbot with his method [Talbot, Saltzman, Wixom, and Wolfe (1945)]. The normal range is 0.10 to 0.35 mg per 24 hours of 11-oxy corticosteroids (11-oxy steroids).

† The level fell from 200-300 units per 24 hours to less than 6 units per 24 hours. Normal range of FSH excretion is 6 to 50 mouse units per 24 hours [Klinefelter, Albright, and Griswold (1943)].

h The urinary 17 ketosteroid excretion showed a moderate decrease with estradiol

2 Androgens in the two forms used (testosterone propionate and methyl testosterone) likewise decreased the calcium and phosphorus excretions in the types of osteoporosis studied (post menopausal and senile) Additional observations on androgen therapy follow

a As in the case of estrogens the fecal as well as the urinary calcium and phosphorus excretions were decreased the effect of the therapy on the calcium metabolism was slow in reaching its maximum and persisted for a long time after cessation of therapy the serum phosphorus levels tended to fall, and the serum alkaline phosphatase levels failed to rise

b In contrast to estrogens, androgens produced a marked and prolonged decrease in the urinary nitrogen excretion

c The range of dosages employed was for testosterone propionate 25 mg daily to 25 mg every other day intramuscularly, and for methyl testosterone 40 to 100 mg daily by mouth

d Methyl testosterone appeared to be as effective as testosterone propionate

3 Progesterone in the dosages of 10, 25, and 100 mg daily, had no definite effect on calcium metabolism whether given alone or in combination with estrogen

4 The effect on the calcium metabolism of estrogen and androgen in combination was greater than that of either alone in the patients with post menopausal or senile osteoporosis

(2) Certain Therapeutic Aspects Concerning Post Menopausal Osteoporosis

A large number of cases, many complicated by fractures, have been treated with estrogens alone and in combination with testosterone compounds during the past five years. As a group these patients have responded very satisfactorily. Within weeks to months, the pain in the spine and other bones usually has been considerably or completely eliminated. There has frequently been an increase in weight, apparently an increase in the thickness of the skin and an improvement in the general well being. Whereas the study is impossible to control, we have the impression that fractures, especially of the hip, in old ladies have responded better than they would have otherwise. However, in spite of these favorable clinical manifestations, it has been difficult to produce undisputed evidence that the bones (excluding fracture sites) as visualized by x ray have become more dense than before the therapy was instituted. Never-

theless, the recent films of several of the longest treated cases are fairly convincing.

Dosages have ranged as follows: diethylstilbestrol 0.5 to 1 mg daily p.o., estrone sulfate* 2.50 to 3.75 mg daily p.o., estradiol benzoate 1.66 to 3.32 mg three times a week i.m., and estradiol dipropionate 5 mg weekly i.m. A few patients have been treated by implantation of pellets. Continuous estrogenic effect on the endometrium leads to metropathy; this can be prevented by interrupting the estrogenic therapy periodically (every 4 to 6 weeks for 7 to 10 days) which allows for estrogen withdrawal bleeding; essentially the same thing can be accomplished by administering at regular intervals (every 4 to 6 weeks) a course of progesterone (5 mg daily i.m. for 5 days) or of anhydro-hydroxy progesterone (40 to 60 mg daily p.o. for 5 days), which results on cessation of therapy in progestin withdrawal menstruation. Testosterone compounds cannot be given in most patients with the impunity suggested from Metabolic Study No. 4; this woman was remarkably free from the masculinizing effect of such medication. Most women will not tolerate more than 200 mg per month of testosterone propionate. We usually give some form of testosterone at least for the first six to twelve weeks. We have prescribed methyl testosterone 10 to 20 mg daily p.o., or testosterone propionate 10 to 20 or 25 mg a week i.m. One of the more successful methods of administering testosterone compounds to these patients is to implant one or two pellets of testosterone [75 mg each (Schering)] every three to four months. As has been pointed out by Greenblatt (1947) therapy with testosterone compounds also reduces the amount of estrogen withdrawal bleeding.

Since many of the steroids cause sodium retention, the above endocrine therapy may cause edema in certain elderly patients, especially if they have low serum protein levels. If this is not controlled by a low sodium chloride diet, and/or ammonium chloride, the steroid therapy may have to be modified.

Because of the possible danger that continued estrogenic medication may lead to cancer, it has been our practice to interrupt the medication for 7 to 10 days every 4 to 6 weeks even though the uterus is out. An examination of the vaginal smear every six months provides a further safeguard [Fremont-Smith, Graham, Janzen, and Meigs (1945)]. If the uterus is in, a record should be kept of the vaginal bleeding; any bleeding not according to plan (that is, not following estrogen or progesterone withdrawal) should promptly be investigated further.

Since osteoporosis is a deficiency in bone matrix protoplasm, a high protein diet is probably indicated, since it is not a disease of calcium and

* Conjugated equine estrogens (Premarin) (Ayerst, McKenney and Harrison Ltd., New York, N. Y.)

phosphorus metabolism excessively high intakes of these minerals and of vitamin D are probably not indicated. Prolonged immobilization should of course be avoided if possible because of the danger of superimposed atrophy of disuse (see p. 147).

(3) Ovarian Agenesis and Other Forms of Congenital Hypoestrogenism

If the absence of estrogen production after the menopause leads to osteoporosis it follows that absence of estrogen from birth on in females due to some congenital disorder should likewise lead to osteoporosis beginning at about the time estrogen should appear that is at puberty. This is true. Thus in ovarian agenesis [Albright, Smith and Fraser (1942)]

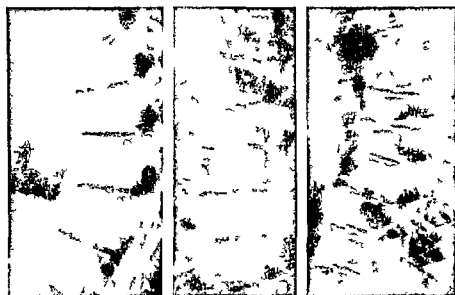


Fig. 7. X-ray Films Showing So Called "Etiophysitis"

For discussion on see text. A—Case 4, B—Case 9, and C—Case 11 from Albright, Smith and Fraser (1942).

panhypopituitarism [Fraser and Smith (1941)] and a syndrome characterized by a selective lack of the follicle stimulating hormone of the pituitary gland [Klinefelter, Albright and Griswold (1943)] one finds osteoporosis along with other manifestations of precocious senility. It should be remembered, however, that such patients have delayed union of the epiphyses; in the spine this leads to deformities which the roentgenologists for no particularly good reason have termed epiphysitis (see Fig. 77). The resulting deformities may lead to immobilization of the back and to secondary disuse atrophy (see p. 147). In males eunuchoidism leads to an analogous situation.

The treatment, of course, should include estrogen therapy, to which these patients respond very well

(E) *Osteoporosis of Old Age*

Most of the changes of old age are, in the final analysis, due to atrophy, in terms of the skeleton atrophy is osteoporosis. How much of the atrophy of old age is due to underfunction of the steroid producing glands, and how much is due to old age *per se* are, as yet, unanswered questions. That steroids may play an important role is suggested by the increased incidence of senile osteoporosis in women compared with men (cf. old women with fractured hips). In many cases osteoporosis of disuse, of malnutrition, of the post menopausal state, and of senility are inseparably superimposed.

Metabolic Study No. 6

Case No. 13 Senile Osteoporosis in a Male of 72, Testosterone Propionate and Estradiol Benzoate Therapy

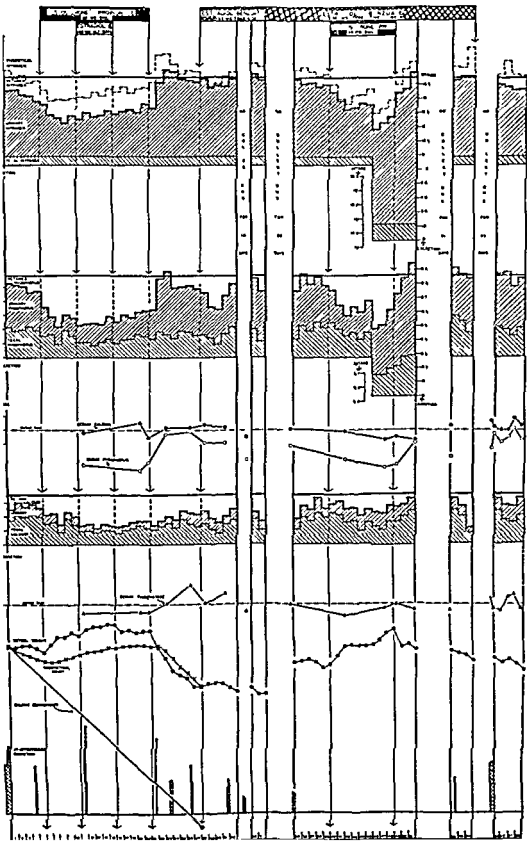
M. H. (M. G. H. 278511), a male of 72 years developed pain in the back after a minor injury one year before admission (1-1-41). The symptoms persisted in spite of local therapy and he was referred to the hospital. The only abnormal findings on physical examination were a thin skin and deformities of the spine; his blood pressure was 140/80. X-ray examination of the spine showed marked decrease in density of the vertebrae with a cod fish deformity of some and wedging or collapse of others. Laboratory studies: serum calcium 10.0 mg. per 100 cc., serum phosphorus 3.1 mg. per 100 cc., serum alkaline phosphatase 4.2 Bodansky units, serum total protein 7.0 gm. per 100 cc., serum non protein nitrogen 18 mg. per 100 cc., urinary 17 ketosteroid excretion 7.2 and 6.9 mg. per 24 hours, follicle stimulating hormone excretion in the urine normal, gastric acidity normal. The normal level of the follicle stimulating hormone excretion is against the osteoporosis having been due to the 'male climacteric'. This case has been mentioned in previous communications [Albright (1912-1913), Reifenstein, Albright, Parson, and Bloomberg (1942), Reifenstein, Albright and Wells (1945) and Reifenstein and Albright (1947) Case 6].

The metabolic data of Case No. 13, which comprise studies done on 220 of 530 consecutive days, are shown in Fig. 78. The study, conducted in five day

Fig. 78 Metabolic Study on Effect of Testosterone Propionate Alone and in Combination with Estradiol Benzoate and *Vice Versa* on a Male Patient (M. H. M. G. H. 278511) with Senile Osteoporosis. Case No. 13

For explanation of construction of chart see Appendix, page 309

Note that testosterone propionate had an effect on calcium metabolism similar to that of estradiol benzoate with regard to both fecal and urinary excretions; that estradiol benzoate therapy added to that of testosterone propionate further improved the calcium balance; that testosterone propionate had a greater effect on nitrogen and phosphorus metabolism than did estradiol benzoate. Periods 1 through 22 are those analyzed in Fig. 155, page 304. [From Reifenstein and Albright (1947) and Albright (1947a).]



periods, consisted of (1) five control periods, (2) five periods on testosterone propionate, 25 mg by injection daily, (3) five periods in which estradiol benzoate 1.66 mg by injection on alternate days was added to the testosterone propionate therapy, (4) five periods back on testosterone propionate alone, (5) seven control periods off all medication, (6) five periods on estradiol benzoate 1.66 mg by injection twice daily, (7) 10 days without collections on the same medication, (8) two more periods on the same medication, (9) 93 days at home on estradiol benzoate 3.32 mg by injection three times a week, (10) five periods on the same therapy, (11) nine periods in which testosterone propionate 25 mg intramuscularly daily was added to the estradiol benzoate therapy during the last three of which periods the intakes of nitrogen and phosphorus were markedly increased (12) three periods on the same diet and the same estradiol benzoate therapy but off testosterone propionate therapy, (13) 91 days at home on the same estradiol benzoate therapy, (14) three periods on the original diet without change in estradiol benzoate therapy, (15) 43 days at home off all medication, and finally (16) four control periods on the original diet without medication.

Fig 78 is self explanatory. The observations as a whole confirm those noted under post menopausal osteoporosis (see p 158). To be noted especially in Fig 78 are (1) the marked reduction in nitrogen, phosphorus and calcium excretions with testosterone therapy, (2) the lack of rebound in the calcium excretion as opposed to those of nitrogen and phosphorus following cessation of testosterone therapy, (3) the further reduction in the phosphorus and especially in the calcium excretion but not in the nitrogen excretion when estradiol benzoate therapy was added to testosterone propionate therapy (periods 16-20), (4) the improvement in all three balances when testosterone propionate was added to estradiol benzoate therapy (periods 40-45), (5) the reduction in the fecal as well as the urinary calcium and phosphorus excretions by both testosterone propionate and estradiol benzoate therapy, (6) the effect of both testosterone propionate and estradiol benzoate therapy in lowering the serum phosphorus level, (7) the failure of marked increases in the nitrogen and phosphorus balances as the result of increases in the diet to affect the calcium balance (periods 46, 47, 48), (8) the absence of any significant change in the serum phosphatase and calcium levels, (9) the fall in the urinary 17 ketosteroid level with estradiol benzoate therapy, and (10) the tendency to accumulate extracellular fluid during both testosterone propionate and estradiol benzoate therapy as suggested by the theoretical weight curves, with a prompt loss following the cessation of therapy.

A more detailed analysis of the nitrogen, phosphorus and calcium balances during periods 6 through 20 when the patient was receiving steroid hormone therapy is shown in Fig 155 (see p 304). It will be seen that there is close agreement between the measured phosphorus balance and the theoretical phosphorus balance (see p 303) based on nitrogen and calcium balances. This is evidence that nearly all of the phosphorus retained as a result of testosterone propionate and estradiol benzoate therapy is retained either in bone or in protoplasm [Reifenstein, Albright, and Wells (1945)].

The treatment of senile osteoporosis is essentially the same as that of post menopausal osteoporosis (see p 159). If testosterone is used in old men, the prostate should be watched and estrogen therapy should probably be given at the same time, since Huggins and Clark (1940) have shown that estrogen neutralizes the stimulating action of testosterone on the prostate.

(F) *Osteoporosis of Cushing's Syndrome*

The important clinical features of Cushing's syndrome are (1) marked muscular weakness, (2) osteoporosis notably of the spine and, in children, cessation of skeletal growth, (3) a thin red skin which is subject to striae formation and easy bruisability, (4) hirsutism without other evidence of virilism, (5) a redistribution of fat deposits resulting in thin arms and legs a "moon face", and a "Buffalo hump", (6) hypertension, (7) amenorrhea and loss of libido, (8) acne, (9) insulin resistant diabetes, (10) atrophy of lymphoid tissue with lymphocytopenia and polymorphonuclear leukocytosis, and (11) a disturbance in electrolyte metabolism with a tendency to high serum sodium and bicarbonate levels coupled with low serum potassium and chloride levels.

The immediate cause of the syndrome is an overproduction of the adrenal cortical 'Sugar' or 'S' hormone [Albright, Parson, and Bloomberg (1941), Albright (1942-1943), and Albright (1947a)] Three new pieces of evidence can now be added to support this contention (a) Talbot, Saltzman, Wixom, and Wolfe (1945) find high titers of "11 oxy steroids" in the urine of patients with Cushing's syndrome For example, in our most recent case they found a value of 5+ mg/24 hours whereas the upper limit of normal is about 0.3 to 0.4 mg/24 hours (b) The earlier observations of Anderson, Haymaker, and Joseph (1938), and of Weil and Browne (1939, 1940), who found by biological methods increased amounts of "S" hormone in the urine of patients with Cushing's syndrome can now be confirmed by improved techniques Thus, using a modification of the Dobriner, Lieberman, and Eggleston (1945) adaptation to mice [see also Eggleston, Dobriner, and Rhoads (1941)] of the Reinecke and Kendall (1942) test for 'S' hormone on rats, Miss Grace Griswold in our laboratory was able to demonstrate in this same patient with Cushing's syndrome 72 mouse units/24 hours, whereas the upper limit of normal is about 6 mouse units/24 hours (c) It is now quite clear, from the work of Dougherty and White (1941) and others, that the 'S' hormone causes disintegration of the thymus and lymphoid tissue with a resulting decrease in the lymphocyte count, De La Balze, Reifstein, and Albright (1946) were able to demonstrate a marked lymphocytopenia in ten cases of Cushing's syndrome as compared with a lymphocytosis in twenty cases of Addison's disease When this new evidence is added to the old, we think it is safe to conclude that whatever bone changes are found in Cushing's syndrome are the result of an excess production of "S" hormone

In many cases the overproduction of 'S' hormone is due to a cancer of the adrenal gland In the non cancer cases, the cause of the overproduction is not clear, it may result from increased production of adreno-cortico-trophic hormone

The 'Sugar' hormone besides causing atrophy of the thymus and lymphoid tissue has a profound but not clearly understood effect upon carbohy-

drate, protein, and fat metabolisms. It unquestionably antagonizes the action of insulin. Many authors have been satisfied to summarize its metabolic effect by the assertion that it facilitates the conversion of protein into sugar (gluconeogenesis).

It has been our concept [Albright (1942-1943)] that protoplasm in general, like the protoplasmic matrix of bone (see p 5), is constantly being anabolized and catabolized at one and the same time, a factor which increases catabolism would lead to very much the same net result as a factor which inhibits anabolism, but there would be some differences, it is our belief that the 'S' hormone is anti-anabolic rather than catabolic. We will cite six pieces of evidence. (a) An inability to attain a positive nitrogen balance rather than a propensity to go into a negative nitrogen balance would be characteristic of an individual suffering from an excess of an anti-anabolic principle, studies on patients with Cushing's syndrome have seldom revealed markedly negative nitrogen balances. (b) The minimal nitrogen excretion (excretion on a high-calorie, low protein diet) is not high in Cushing's syndrome [Albright (1942-1943)], this evidence is against there being an excess of a catabolic principle in Cushing's syndrome. (c) The negative nitrogen balance which follows operations, injuries, and burns is little influenced by a moderate excess of nitrogen in the intake, it, too, is thought to be due to an excess of the 'S' hormone (see p 185), if the 'S' hormone were catabolic one should be able to compensate for it by supplying an excess of the materials needed for anabolism. (d) There are certain anabolic processes which are irreversible and thus cannot be wiped out by catabolism,—for example, growth at an epiphyseal cartilage, if the 'S' hormone were a catabolic principle, it should not inhibit epiphyseal growth a purely anabolic function, Wells and Kendall (1940) obtained cessation of growth in rats with Compound E and corticosterone, both 'S' hormones. Becks, Simpson, Li, and Evans (1944) likewise obtained cessation of growth (achondrogenesis) with adreno-corticotrophic hormone, finally a patient of ten years and eleven months with Cushing's syndrome studied in our clinic showed almost complete cessation of growth during the active stage of the disease (see Fig 79 and 80). (e) Becks, Simpson, Marx, Li, and Evans (1944) working with hypophysectomized rats found that growth hormone activated the epiphyseal cartilage and thus promoted endochondral bone formation, that adreno-corticotrophic hormone given together with the growth hormone prevented the effect of the growth hormone, it is quite clear from these experiments that the 'S' hormone, produced as a result of stimulation of the adrenal cortex with the adreno-corticotrophic hormone, inhibited the anabolic action of the growth hormone and is therefore anti-anabolic. (f) A study of the one tissue where it is possible to distinguish under the microscope between anti-anabolism and catabolism histologically, namely bone shows very clearly that the disturbance in

the bone in Cushing's syndrome is an anti anabolic one, thus one finds osteoporosis, where the primary difficulty is lack of bone formation by the osteoblasts, not osteitis fibro-a generalisata, where the initial step is the resorption of bone

There are several hormones other than the 'S' hormone that are made by the adrenal cortex. A short discussion of the "Nitrogen" or "N" hormone is necessary for the understanding of the rationale of treatment with testosterone compounds. The evidence has been presented [Albright (1942-1943), Albright (1947a)] that the normal adrenal cortex produces a hormone (the 'N' hormone) with properties very similar to testosterone. This hormone is not produced until puberty, it governs the growth of axillary hair in women, it has an anabolic action on protoplasm similar to testosterone, and it is responsible entirely in women and partially in men for the 17 ketosteroids excreted in the urine.

The adreno-genital syndrome offers an excellent opportunity to study the effect of an excess of "N" hormone on osteogenesis. Children with this affliction grow much more rapidly in every way than do normal children (see Fig 79 and 80) but, due to early closure of the epiphyses, end up by being normal in height or slightly short. The bony structure itself of the skeleton of such children is dense but probably not pathologically so. Adults who develop this condition do not develop the characteristics of acromegaly, this suggests that periosteal bone is not stimulated by the 'N' hormone.

It appears, therefore, that the "N" hormone is opposite in its action to the 'S' hormone as regards endochondral and probably endosteal bone formation. In both of these respects "N" hormone is like testosterone. Furthermore, "N" hormone is similar to growth hormone as regards epiphyseal growth, but not as regards membranous bone formation.

It follows from the above discussion that an excess of "N" hormone should neutralize an excess of 'S' hormone. In the absence of a preparation of "N" hormone, it became of interest to study the effects of testosterone compounds on cases with hyperadrenocorticism with respect to the 'S' hormone (Cushing's syndrome). Fig 81 shows in diagrammatic form the changes in the disordered homeostasis to be anticipated by such therapy.

The following two metabolic studies serve to illustrate some of the points just discussed.

Metabolic Study No 7

Case No 14 Cushing's Syndrome with Osteoporosis, Nephrolithiasis, Estradiol Benzoate and Testosterone Propionate Therapy

B A (NIG H 7432) a 25 year-old single girl of Portuguese descent has been followed at the Massachusetts General Hospital for five years with the diagnosis of Cushing's syndrome. Her chief complaint when first seen was 'amenorrhoea

for two years." She also revealed that she had been gaining weight about the face, neck, and abdomen, and that her face had become ruddy and more hairy

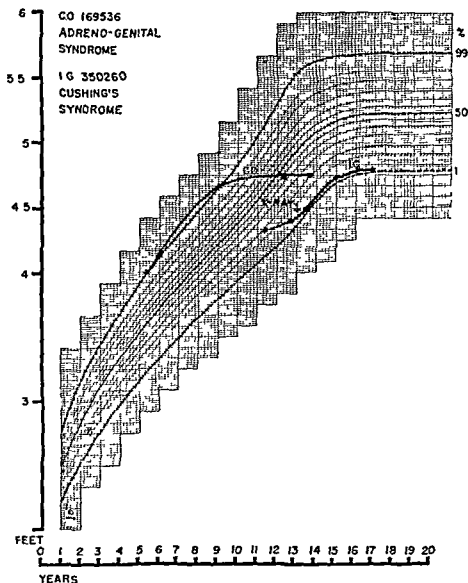


Fig 79 Chart to Contrast the Growth of Patient (C O, M G H 169536) with Adreno Genital Syndrome with That of Patient (I G, M G H 350260) with Cushing's Syndrome.

For discussion, see text [From Albright, Reifenstein and Forbes (1946)]

than before. In addition, she had noticed easy bruisability and had had recurrent skin infections

On examination, she had the typical round, full, plethoric facies of Cushing's syndrome, with excessive facial and abdominal hair. The skin appeared atrophic with purplish striae and numerous visible dilated subcutaneous blood vessels.

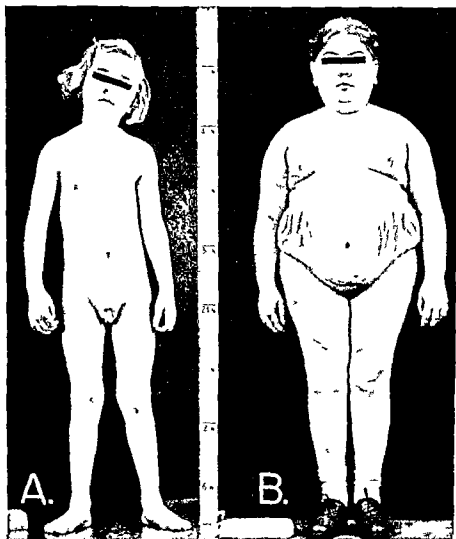


Fig. 80 Photographs to Contrast a Patient with Adreno Genital Syndrome with a Patient with Cushing's Syndrome

A = Patient C O (N G H 169536) at 5 years and 6 months with adrenogenital syndrome, B = Patient I G (N G H 350260) at 11 years and 10 months with Cushing's syndrome. Scale applies to both photographs. [From Albright (1942-1943)]

There were scars of old infections on the legs. The optic fundi showed some old hemorrhage and exudate. The heart was not enlarged. Blood pressure varied from 130/90 to 170/110. The clitoris was not enlarged.

Laboratory studies included negative Hinton test result, red blood cell count 4.8 million, hemoglobin 95%, urine, a trace of albumin and intermittent glycosuria, *B. coli* and *Staphylococcus albus* on culture blood chemistry, not remarkable, sodium normal. Glucose tolerance test showed a failure to return to normal four hours after administration of glucose. Combined glucose and insulin test result paralleled that of the glucose tolerance test. Several basal metabolic rate tests were normal. Electrocardiogram showed evidence of myo-

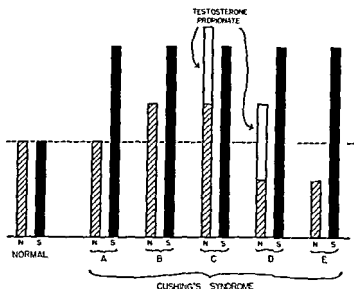


Fig S1 Schematic Diagram to Illustrate Authors' Interpretation of Relationship of 'N' Hormone Production to 'S' Hormone Production in Cushing's Syndrome Before and After Testosterone Propionate Therapy

A = pure form of Cushing's syndrome without compensation, B = Cushing's syndrome with compensatory rise of the "N" hormone, C = Cushing's syndrome under testosterone propionate therapy, D = same as C except for decrease in endogenous "N" hormone production which results after exogenous 'N' hormone therapy has been instituted, E = effect of withdrawal of exogenous 'N' hormone therapy. It will be noted in E that the imbalance between the 'N' hormone and 'S' hormone production is greater than it was before therapy was instituted which may explain the marked rebound in nitrogen excretion which occurs when testosterone propionate therapy is omitted in Cushing's syndrome. [From Albright (194? 1943)]

cardial damage. Follicle stimulating hormone assay on urine was negative for 10 mouse units per 100 cc (normal). The 17 ketosteroids in the urine varied from 8 to 14 mg per 24 hours before treatment. X rays showed marked osteoporosis with numerous fractured vertebrae and bilateral kidney stones.

Both adrenals were explored. Biopsied sections were said to show no abnormalities. She received three courses of x ray irradiation to the pituitary. There was a remission for about a year, with return of regular menses after the first course. The last two courses had no effect. Kidney stones required operation twice.

The patient showed marked improvement on testosterone therapy, as discussed below. It is of real interest that after cessation of therapy her improvement continued and it was found that the abnormality in sugar metabolism had entirely disappeared. For two years after cessation of therapy, her menses were normal and she presented no evidence of a recurrence. Subsequently she exhibited increasingly severe cardiac disease, from which she ultimately died. This case has been mentioned in previous communications [Albright, Parson, and Bloomberg (1941) *Case 1*, Fraser, Forbes, Albright, Sulkowitch, and Reifenshtein (1941) *Case 37*, Albright (1942-1943), Reifenshtein, Albright, and Wells (1945), Albright (1947a), and Reifenshtein, and Albright (1947) *Case 10*].

The metabolic data of Case No. 14 are shown in Fig. 82. The study covers 37 five day periods obtained on four hospital admissions. The data in Fig. 82 are self explanatory. It should first be noted that the phosphorus balance corresponds reasonably well with the sum of the nitrogen and calcium balances during the last 23 periods but not the first 14. This suggests some constant error in the first 14 periods, probably in the value for the nitrogen intake. A more detailed analysis to emphasize the close agreement between the nitrogen, potassium, phosphorus, and sulphur balances of periods 15 through 33 is shown in Fig. 156 (see p. 306). It will be seen that there is a close correspondence between the measured and the theoretical nitrogen balances based on potassium, phosphorus, and sulphur. This is evidence that testosterone propionate therapy induced a retention of nitrogen, potassium, phosphorus and sulphur in the proportions that exist in muscle protoplasm [Reifenshtein, Albright, and Wells (1945)].

Other observations to be underlined in Fig. 82 are (1) the marked decrease in the urinary nitrogen, phosphorus and calcium excretions with testosterone propionate therapy, (2) the marked rise in the serum phosphatase level when the increase in calcium balance became appreciable (see periods 30 through 33). Whereas Fig. 82 suggests that insulin had a marked effect on the calcium balance (see periods 28 and 29) the authors are inclined to discount this because of the essentially negative result in a second patient with Cushing's syndrome so treated [Reifenshtein and Albright (1943)].

Metabolic Study No. 8

Case No. 15. Cushing's Syndrome with Osteoporosis, Estradiol Benzoate, Testosterone Propionate, and Methyl Testosterone Therapy.

R. B. (M. G. H. 3397), a 50 year old native mother of three children was followed at the Massachusetts General Hospital for four and a half years with the diagnosis of Cushing's syndrome. Her chief complaint when first seen was "marked weakness for five years". She had had amenorrhea without hot flashes for five years, during this time she had noticed increasing facial and body hirsutism. Glycosuria had been noted two years before admission and had been treated with diet. She complained also of recurrent skin infections and brittle nails. There had been a gradual weight loss of 86 pounds during the four years preceding her admission to the hospital.

On examination, she presented the typical plethoric appearance. The skin showed atrophy, striae, dilated subcutaneous vessels, and easy bruisability. The optic fundi showed irregular arterioles, hemorrhages, and exudate. The

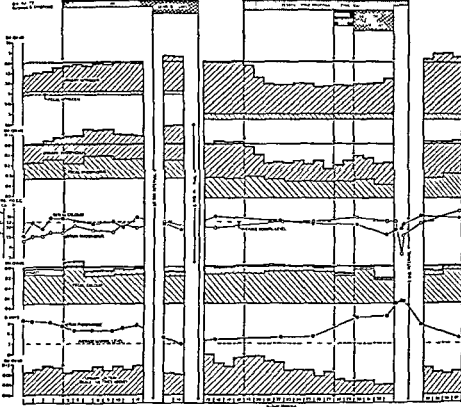


Fig 82 Metabolic Study on Effect of Estradiol Benzoate and Testosterone Propionate on a Female Patient (B V , M G H 74372) with Osteoporosis due to Cushing's Syndrome, Case No 14

For explanation of construction of chart see Appendix, page 309

At the bottom of the chart, the urinary calcium is shown separately on an enlarged scale

Note that estradiol benzoate did have a slightly beneficial effect on the calcium balance (compare periods 13 and 14 with periods 1 through 4) in spite of an adverse effect on the nitrogen and phosphorus balances. Note markedly beneficial effect of testosterone propionate on nitrogen, phosphorus, and calcium balances, note steady decrease in urinary calcium excretion shown in magnified form at the bottom of the chart, throughout testosterone propionate therapy with accompanying rise in serum phosphatase level. Note that the addition of estradiol benzoate to the testosterone propionate therapy (periods 30 through 33) apparently improved the calcium balance. Periods 15 through 33 are those analyzed in Fig 156, page 306 [From Reifsteina and Albright (1947), and Albright (1947a), recharted from Albright, Parson and Bloomberg (1941)]

facial hirsutism was striking. The abdomen and breasts were flabby and pendulous. The heart was not enlarged. Blood pressure varied from 130/75 to 160/100. The clitoris was not enlarged.

Laboratory studies included negative Hinton test result, red blood cell counts varied from 4.1 to 5.5 million, hemoglobin was 90 to 100 per cent, urine—no albumin, intermittent glycosuria. Blood chemistry values were not remarkable. Serum sodium values were 142 and 142.5 mEq per liter. Glucose tolerance tests showed a failure to return to fasting level four hours after the administration of glucose. Combined glucose and insulin tolerance tests paralleled these figures. The basal metabolic rate was normal. Follicle stimulating hormone assayed for 10 mouse units per 100 cc. was weakly positive once and negative twice, the 17 ketosteroids in the urine varied from 18 to 36 mg. per 24 hours. Electrocardiogram showed evidence of myocardial damage. X ray showed extensive osteoporosis with numerous fractured vertebrae.

Both adrenals were explored. Biopsied specimens were not considered abnormal grossly or microscopically. The patient received two courses of x ray treatment to the pituitary, and one course to the thymus without apparent effect. She showed an amazing clinical improvement on testosterone therapy and was able to walk a few steps without support after three years of complete invalidism in bed. This case has been mentioned in previous communications [Albright, Parson, and Bloomberg (1941) *Case 2*, Fraser, Forbes, Albright, Sulkowitch, and Reifenstein (1941) *Case 36*, Albright (1942-1943) Reifenstein, Albright, and Wells (1945), Reifenstein, Forbes, Albright, Donaldson, and Carroll (1945) *Case 2*, Albright (1947a), and Reifenstein and Albright (1947) *Case 11*].

The metabolic data of Case No. 15 are shown in Fig. 83. The study covers 55 five day periods obtained on six hospital admissions. The data in Fig. 83 are self explanatory. It should first be noted that the phosphorus balance corresponds reasonably well with the sum of the nitrogen and calcium balances throughout.

Other points to be noted in Fig. 83 are: (1) the lowering of the urinary nitrogen, phosphorus, and calcium excretions with testosterone propionate therapy (periods 10 through 18, and 23 through 36) and with methyl testosterone therapy (periods 50 through 55), (2) the fact that the fecal phosphorus and calcium excretions were also lowered with these two testosterone compounds, (3) the quick rebound in the nitrogen and phosphorus but not in the calcium metabolism on cessation of testosterone propionate therapy (see periods 19 through 22), (4) the steady improvement in calcium metabolism with continued administration of testosterone propionate therapy, (5) the elevation of the serum phosphatase with improvement in the calcium balance, and (6) the rise in the serum phosphorus level following omission of estradiol benzoate therapy in period 6. The marked improvement in calcium balance in periods 29 through 36 is probably to be attributed to continued testosterone propionate therapy, but the initiation of vitamin D therapy in period 29 makes the exact interpretation difficult. Dehydroisoandrosterone acetate in periods 42-46 did not prevent the rebound in nitrogen and phosphorus metabolisms for omission of testosterone propionate therapy.

Testosterone propionate had a markedly beneficial effect on the nitrogen, phosphorus, and calcium balances in both patients, the effect on the calcium balance seemed to increase with duration of treatment (compare in Fig. 83, periods 10 to 14 with periods 15 to 18). Furthermore, with the improvement in calcium balance with testosterone propionate therapy, there was a rise in the alkaline phosphatase level. Methyl testosterone had a similar

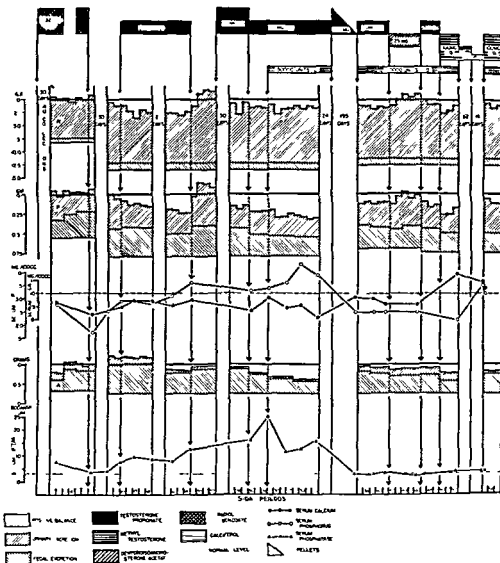


Fig 83 Metabolic Study on Effect of Estradiol Benzoate Testosterone Propionate and Methyl Testosterone on a Female Patient (R. B. MGH 339) with Osteoporosis due to Cushing's Syndrome Case No 15

For explanation of construction of chart see Appendix page 309

Whereas the data are not very satisfactory whereon to judge the effect of estradiol benzoate note in period 8 that the calcium balance became negative 40 days after cessation of estradiol benzoate therapy Note that testosterone propionate and methyl testosterone had an almost immediately beneficial effect on the nitrogen balance whereas their effect on the calcium balance was cumulative (compare periods 10 through 14 with periods 15 through 18) Note that the serum phosphatase level continued to rise as the calcium balance improved which suggests that the osteoblasts were stimulated to increased activity Note that dehydrosoandrosterone acetate was ineffective in inhibiting the rebound in the nitrogen and phosphorus balances on cessation of testosterone propionate therapy (period 43) [From Albright (1947) 1943) Reifenstein and Albright (1947) and Albright (1947a) recharted from Albright, Parson and Bloomberg (1941)]

effect to that of testosterone propionate, dehydroisoandrosterone acetate apparently had no effect. The first patient (see Fig 82) received testosterone propionate, 25 mg daily for 11 five-day metabolic periods. It was calculated that she retained nitrogen at the rate of 8 per cent per month of the nitrogen content of the entire body of a normal individual of her size, or about 19 per cent for the 70 days during which she received the medication. With this positive nitrogen balance there was likewise a marked improvement in her calcium balance with an elevation in the serum phosphatase level, the index of osteoblastic activity. It will be seen, as discussed above, that her phosphorus retention when corrected for the amount retained with calcium in the bones ($\text{Ca/P} = \text{circa } 20$) was about proportional to the nitrogen retention if one uses the ratio of nitrogen to phosphorus in muscle tissue ($\text{N/P} = \text{circa } 15$), it will be remembered, furthermore, that potassium and sulphur were also retained proportionately to their ratios with nitrogen in muscle. It is suggested from these observations that testosterone therapy in Cushing's syndrome stimulates the anabolism of protoplasm, which, in bone tissue, means stimulation of osteoblasts to lay down osteoid.

Although several investigators, including Dunn (1938) and Rakoff, Cantarow, and Paschke (1941), have reported a beneficial action from a purely clinical point of view of estrogens in the treatment of Cushing's syndrome, and although the osteoporosis in this condition is very similar to that seen in the post menopausal state, Albright, Parson, and Bloomberg (1941) concluded from metabolic studies (calcium, phosphorus and nitrogen) on two patients that estrogen was without effect. Perloff, Rose and Sunderman (1943) also reported an inconclusive effect of estrogen on the calcium metabolism in Cushing's syndrome. A further analysis [Albright (1947)] of the data of Albright, Parson, and Bloomberg (1941), however shows that their conclusion is not justified. It is true that estrogen has no beneficial effect on the nitrogen balance which was in marked contrast to the effect of testosterone propionate. On the other hand, it is quite clear that estrogen administration did benefit the calcium balance. Thus, in their patient No 1 (see Fig 82), estrogen therapy while apparently adversely affecting the nitrogen balance, increased the calcium balance later in the same patient the addition of estrogen administration to that of testosterone propionate further improved the calcium balance. In their patient No 2 (see Fig 83), estrogen therapy was started before the metabolic study was initiated, so its effect is hard to evaluate, none the less, further metabolic studies undertaken 35 days after omitting estrogen show that the calcium balance had changed from a positive to a negative one.

The 'S' hormone as judged by its effect on patients with Cushing's syndrome has a marked predilection for the spine and pelvis. Conversely,

if one were to recover from Cushing's syndrome, one would expect to see changes in the spine and pelvis and no changes in the extremities

In Fig 84, 85, 86, and 87 are shown the x ray findings of the lumbar and



Fig 84 Photograph of an x ray Film of Lower Lumbar Vertebrae of a Girl (I G M G H 350260) with Severe Osteoporosis due to Cushing's Syndrome Before Recovery

Film taken June 6, 1942 Note that the vertebrae except for their end plates are no denser than the intervertebral disks note also that the intervertebral disks have expanded at the expense of vertebrae so that they are now wider than the vertebrae themselves [From Albright (1942-1943), Albright, Reifenstein, and Forbes (1946) and Albright (1947a)]

lower thoracic spine of a female patient [I G , M G H 350260, a 15 year old girl at the time of the second x ray (7 10-45)] before and approximately 15 months after the cessation of the activity of her Cushing's syndrome A more detailed case history will appear elsewhere, suffice it to say that the

agent responsible for overcoming the activity is not definitely known. The improvement may have been spontaneous, it may have been the result of testosterone therapy, it may have been the result of x-ray irradiation.



Fig. 85 Photograph of an X-ray Film of Lower Lumbar Vertebrae of a Girl (I. G. M. G. H. 350260) with Severe Osteoporosis Approximately Fifteen Months After Recovery from Cushing's Syndrome (cf. Fig. 84).

Film taken July 3, 1945. Note that intervertebral discs have been squeezed together and that centers of vertebrae remain radio-translucent in marked contrast to dense bone which has been newly laid down. For further analysis of changes see Fig. 88 and 89. [From Albright, Reifenstein, and Forbes (1946) and Albright (1947a).]

tion of the pituitary gland. The time sequence suggests the last. It will be noted in Fig. 87 that the intervertebral discs were squeezed together again as a result of the growth pressure. In Fig. 88 are depicted in diagrammatic form the authors' interpretation of (A) the normal vertebral find

ings in an individual of her age, (B) the findings in the patient before recovery, and (C) the findings in the patient after recovery Fig 89



Fig 86 Photograph of an X ray Film of Lower Lumbar Vertebrae of a Girl (I G M G H 3:00'60) with Severe Osteoporosis due to Cushing's Syndrome Before Recovery

Film taken June 6 1942 For discussion see legend to Fig 84 [From Albright Reifenstein and Forbes (1946) and Albright (1947a)]

represents a tracing of the vertebrae shown in Fig 84 and 85 together with an analysis of the comparative widths of the vertebrae and intervertebral

discs before and after recovery. Note in Fig 85 and 87 that the marked change in the vertebrae following recovery is almost entirely due to the



Fig 87 Photograph of an X ray Film of Lower Lumbar Vertebrae of a Girl (I G M G II 350760) with Severe Osteoporosis Approximately Fifteen Months After Recovery from Cushing's Syndrome (cf Fig 86)

Film taken July 3, 1915. For discussion see legend to Fig 85. [From Albright, Reifenstein, and Forbes (1916) and Albright (1947a)]

laying down of dense new bone, that bone which existed before recovery remains very osteoporotic. It was only because this patient was still

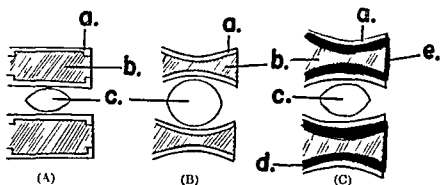


Fig 88 Schematic Representations of Interpretation of Vertebral Changes in Fig 84 and 86 Before Recovery (B) and in Fig 83 and 87 Approximately Fifteen Months After Recovery (C), as Compared with Normal Findings for the Same Age (A)

a = cartilaginous end plate of vertebra b = bony part of vertebra c = nucleus pulposus d = bone laid down after recovery by cartilaginous end plate, and e = bone laid down after recovery by periosteum Note in (B) that nucleus pulposus is expanded at expense of vertebrae because of decreased resistance of vertebrae Note in (C) that nucleus pulposus has been partially squeezed together again by growth pressure [From Albright Reifenshtein and Forbes (1946) and Albright (1947a)]

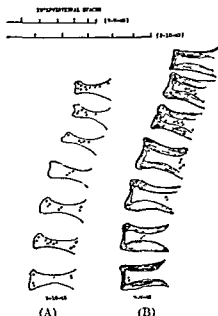


Fig 89 Tracing of Vertebrae Shown in Fig 84 and 83, (A) Vertebrae on 2 10-43 Before Recovery (B) Vertebrae on 7 10-45 Approximately Fifteen Months After Recovery

Note that osteoporotic centers of vertebrae in (B) have same configuration as whole vertebrae on 2 10-43 (A) Note that the sum of the widths of the six intervertebral disks in (B) is shorter than the sum in (A) in spite of the fact that the total length of the vertebrae in (B) is greater than the total length in (A) [From Albright, Reifenshtein, and Forbes (1946) and Albright (1947a)]

growing that these remarkable changes could be demonstrated. It takes a long time in the adult to demonstrate increased density of the vertebrae after alleviation of the activity in Cushing's syndrome. In Fig. 90 is seen the x ray of the wrist taken approximately 15 months after recovery. One



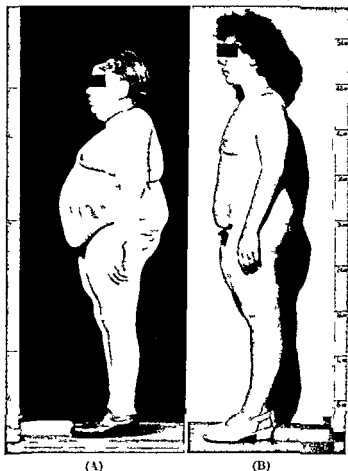
Fig. 90 Photograph of an X-ray Film of the Wrist of a Girl (I. G. M. G. H. 350260) Approximately Fifteen Months after Recovery from Cushing's Syndrome.

Film taken July 3, 1945. Note absence of any change in density of that bone most recently laid down in juxtaposition to the epiphyseal cartilages. [From Albright, Reifenstein, and Forbes (1946), and Albright (1947a).]

is impressed by the lack of a zone of increased density adjacent to the radial epiphyseal cartilage, this is strong evidence that the "S" hormone was not affecting the density of the bone being laid down at the wrist. The remarkable change in the appearance of the patient is shown in Fig. 91 and 92

(G) *Osteoporosis Associated with "Alarm Reaction" ("Adaptation Syndrome" of Selye)*

Selye (1946) studied in animals the anatomical, chemical, and functional adjustments which the body makes to any non specific, noxious stimulus,



(A)

(B)

Fig 91 Photographs to Contrast a Patient with Cushing's Syndrome Before and After Recovery

A = Patient I G (M I G H 350260) in July 1942 at 11 years and 10 months with Cushing's syndrome before recovery, B = the same patient after recovery in July 1945 at 14 years and 10 months. There is a separate scale for each photograph [From Albright, Reifenstein, and Forbes (1946)]

these he grouped together under the term "Adaptation Syndrome". He subdivided this syndrome in animals into three parts (1) "Alarm Reaction", (2) "Stage of Resistance", and (3) "Stage of Exhaustion". He further subdivided the "Alarm Reaction" into the phases of "Shock" and

"Countershock" When this important concept was taken over into clinical medicine, some difficulty was encountered in telling just where one subdivision ended and the next began, this confusion has resulted in the use of the term "Alarm Reaction" as practically synonymous with the

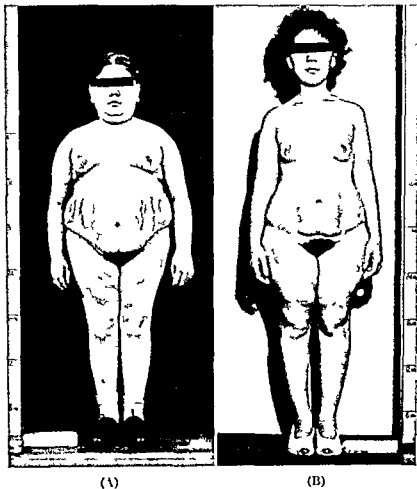


Fig 92 Photographs to Contrast a Patient with Cushing's Syndrome Before and After Recovery (cf Fig 91)

See legend to Fig 91 [From Albright, Reifenstein and Forbes (1946)]

term "Adaptation Syndrome", and the term "Alarm Reaction" is so used here

The most important features of the Alarm Reaction have to do with the alterations in adrenal cortical function. These have been discussed at length by Albright (1942-1943) and by Browne (1944). Briefly stated, we believe as discussed above that the adrenal cortex normally puts out among others two types of steroid hormones (1) the "Nitrogen" or "N" hormone

(see p 167) which stimulates protoplasmic anabolism, and (2) the "Sugar" or "S" hormone (see p 165) which inhibits this anabolic function

Following injury, infection, or anovious stimulus of any kind, there may be a temporary increase in "N" hormone release from the adrenals as judged by the 17-keto-steroid excretion, followed by a decrease to subnormal levels which lasts until convalescence is nearly completed [Forbes, Donaldson, Reifenstein, and Albright (1947)] The "S" hormone production, on the other hand, as judged by its excretion in the urine by biological assay

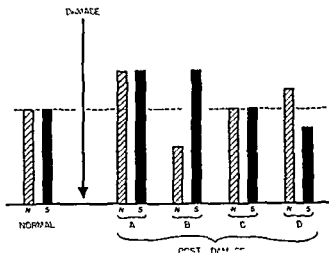


Fig 93 Schematic Diagram to Illustrate the Authors' Interpretation of the Relationship of "N" Hormone Production to "S" Hormone Production in the Normal and During Various Phases of the "Alarm Reaction"

Note in the normal pre damaged state that the "N" hormone and "S" hormone production equal each other or at least are balanced. In A, the immediate period following the damage (circa 12 to 48 hours), there is a discharge of both "N" and "S" hormones from the adrenal cortex, later (B) the "N" hormone production falls below normal while the "S" hormone production continues high, after a period of days, to weeks, to months, depending upon the condition, the levels return to normal (C), finally there may be a slight reversal in the other direction until the body is again built up (D) [From Albright (1912 1943)]

[Venning, Kazmin, and Bell (1946)], and by chemical assay of 11-oxosteroids [Talbot, Saltzman, Wixom, and Wolfe (1945)], rises with the "N" hormone but remains elevated until convalescence is practically completed [Venning (1945)] These various phases of the Alarm Reaction in terms of adrenal cortical function are shown diagrammatically in Fig 93. The early stage in which both the "N" and "S" hormones are released is probably analogous to the end of the Counter-shock Phase in animals, when the adrenal cortices histologically show depletion of lipid granules. The

prolonged phase of low "N" hormone coupled with high "S" hormone production probably corresponds to the Stage of Resistance in animals. In those debilitated patients where a damaging event is not followed by a rise in the 17 ketosteroid excretion preceding the fall, it is probable that previous damaging events have already induced the Stage of Resistance or even the Stage of Exhaustion.

It will be noted that both Cushing's syndrome and the Alarm Reaction have in common a high "S" hormone production. This probably accounts for the following features which these two conditions have in common: decrease in lymphoid tissue, leukocytosis, insulin resistance, muscular weakness, retarded growth, and decreased production of protoplasm in general.

Decreased production of protoplasm in terms of bone economy means osteoporosis. This probably accounts in part for the increased calcium excretion after fractures [Cuthbertson (1930), confirmed by Howard, Parson, and Bigham (1945), and by ourselves (see p 85 and 295)], and after orthopedic operations (see Fig 94). The osteoporosis associated with the Alarm Reaction also responds to estrogen therapy (see Fig 95). In young males estrogen therapy is probably contraindicated because of the danger of testicular tubular sclerosis and resulting sterility.

The whole subject of the relation of the Alarm Reaction to calcium metabolism is complicated by the fact that most damaging events are followed by a certain degree of immobilization and by a decreased food intake, both of which in themselves cause osteoporosis (see p 147 and 149). Indeed, that these two factors may account for the increased calcium excretion following fractures and orthopedic operations is suggested by studies in which individuals were put to bed for a period of time before operation, and were fed intravenously before, during, and after operation so that both the activity and the intake were constant throughout. In these studies, we found the expected loss of nitrogen and phosphorus, and the expected decrease in the 17 ketosteroid excretion, but little change in the calcium excretion after operation [Albright, Reifenstein, and Forbes (1944)]. Such a study is shown in Fig 94.

Metabolic Study No 9

Case No 16 Alarm Reaction due to Spinal Fusion for Spondylolisthesis, 100 per cent Intravenous Feeding

R R (M G H 450196), a 21 year old man in good general health and able to chop wood, had as his only complaint a low back ache occasioned by spondylolisthesis. He entered for a spinal fusion. He was put to bed ten days prior to the operation in order to keep his physical activity constant throughout the study. Starting ten days before the operation he was fed entirely by vein a con-

(see p 167) which stimulates protoplasmic anabolism and (2) the "Sugar" or 'S' hormone (see p 165) which inhibits this anabolic function

Following injury, infection, or anxious stimulus of any kind, there may be a temporary increase in 'N' hormone release from the adrenals as judged by the 17 ketosteroid excretion, followed by a decrease to subnormal levels which lasts until convalescence is nearly completed [Forbes, Donaldson, Reifenstein, and Albright (1947)] The "S" hormone production, on the other hand, as judged by its excretion in the urine by biological assay

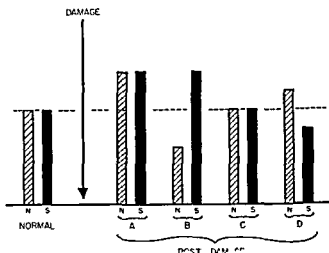


Fig 93 Schematic Diagram to Illustrate the Authors' Interpretation of the Relationship of 'N' Hormone Production to 'S' Hormone Production in the Normal and During Various Phases of the 'Alarm Reaction'

Note in the normal pre damaged state that the 'N' hormone and 'S' hormone production equal each other or at least are balance. In A, the immediate period following the damage (circa 12 to 48 hours), there is a discharge of both 'N' and 'S' hormones from the adrenal cortex, later (B) the 'N' hormone production falls below normal while the 'S' hormone production continues high, after a period of days, to weeks to months, depending upon the condition, the levels return to normal (C), finally there may be a slight reversal in the other direction until the body is again built up (D) [From Albright (1942-1943)]

[Venning, Kazmin, and Bell (1946)], and by chemical assay of 11 oxy steroids [Talbot, Saltzman, Wixom, and Wolfe (1945)], rises with the "N" hormone but remains elevated until convalescence is practically completed [Venning (1945)] These various phases of the Alarm Reaction in terms of adrenal cortical function are shown diagrammatically in Fig 93. The early stage in which both the "N" and "S" hormones are released is probably analogous to the end of the Counter-shock Phase in animals, when the adrenal cortices histologically show depletion of lipid granules. The

prolonged phase of low "N" hormone coupled with high "S" hormone production probably corresponds to the Stage of Resistance in animals. In those debilitated patients where a damaging event is not followed by a rise in the 17 ketosteroid excretion preceding the fall, it is probable that previous damaging events have already induced the Stage of Resistance or even the Stage of Exhaustion.

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Decreased production of protoplasm in terms of bone economy means osteoporosis. This probably accounts in part for the increased calcium excretion after fractures (Cuthbertson (1930), confirmed by Howard, Parson, and Bigham (1945), and by ourselves (see p 85 and 295)), and after orthopedic operations (see Fig 94). The osteoporosis associated with the Alarm Reaction also responds to estrogen therapy (see Fig 9a). In young males estrogen therapy is probably contraindicated because of the danger of testicular tubular sclerosis and resulting sterility.

The whole subject of the relation of the Alarm Reaction to calcium metabolism is complicated by the fact that most damaging events are followed by a certain degree of immobilization and by a decreased food intake, both of which in themselves cause osteoporosis (see p 147 and 149). Indeed, that these two factors may account for the increased calcium excretion following fractures and orthopedic operations is suggested by studies in which individuals were put to bed for a period of time before operation, and were fed intravenously before, during and after operation so that both the activity and the intake were constant throughout. In these studies, we found the expected loss of nitrogen and phosphorus, and the expected decrease in the 17 ketosteroid excretion, but little change in the calcium excretion after operation [Albright, Reifenstein, and Forbes (1944)]. Such a study is shown in Fig 94.

Metabolic Study No 9

Case No 16 Alarm Reaction due to Spinal Fusion for Spondylolisthesis, 100 per cent Intravenous Feeding

R. R. (NIG H 450496), a 24 year old man in good general health and able to chop wood had as his only complaint a low back ache occasioned by spondylolisthesis. He entered for a spinal fusion. He was put to bed ten days prior to the operation in order to keep his physical activity constant throughout the study. Starting ten days before the operation he was fed entirely by vein a con-

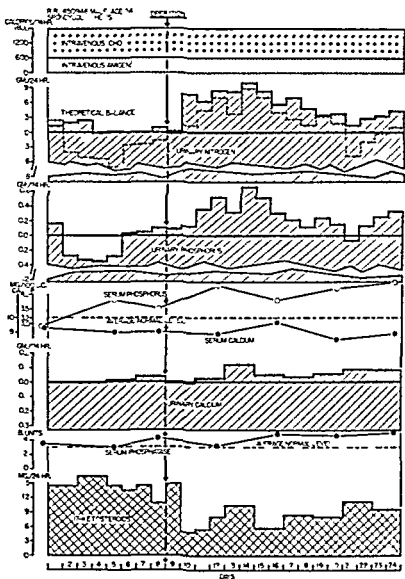


Fig 94 Metabolic Study on Effect of a Thyroid Operation on a Healthy Adult Man (R. R. MGH 45091C) Maintained Exclusively on a Constant Intravenous Intake of Carbohydrate and Casein Hydrolysate (Amigen), Case No. 16

For explanation of construction of chart see Appendix, page 309

Note particularly the markedly negative nitrogen and phosphorus balances immediately following operation in spite of constant intake; the lack of marked change in the calcium balance after the operation, and the shift in the potassium balance toward the negative side although less potassium was lost than would be expected from the nitrogen balance. Note that the chart has been constructed without fecal values since there were virtually no feces during the intravenous alimentation. [From Albright, Reifenstein, and Forbes (1944)]

stant intake, he received nothing by mouth except water as desired. The intravenous infusion mixture was made up as follows: 3000 cc of water containing 300 gm of glucose (1200 Calories), 150 gm of casein hydrolysate (Amigen) (600 Calories), 12.75 gm of sodium chloride in addition to that in the Amigen, 2 gm of potassium chloride in addition to that in the Amigen, 50 mg of vitamin C, 2 mg of vitamin K, 5 mg of vitamin B₁, 75 mg of nicotinamide, 2.5 mg of calcium pantothenate, 5 mg of pyridoxine hydrochloride, and 2 mg of riboflavin. The total caloric intake was 1800 calories. The intravenous infusion was given over a period of 7 to 9 hours each day without complications for a total of 26 consecutive days. The blood lost at operation was measured and replaced by transfusion after the operation. At the end of the experiment the patient was put on a soft solid diet for one meal and then on the routine hospital diet. There were no transitional gastro-intestinal symptoms. This case has been mentioned in a previous communication [Albright, Reifenstein, and Forbes (1944)].

The metabolic study was begun after the patient had been in bed and had been on total intravenous feeding for two days. The metabolic data of Case No. 16 are shown in Fig. 91. The study covers 21 days. The data in Fig. 91 are self-explanatory. During the eight control days the patient was in nitrogen equilibrium, during this period his weight was stationary. Following the operation he remained in nitrogen equilibrium for 24 hours, thereafter he went into a markedly negative nitrogen balance which reached a peak of 9.9 gm. on the sixth post-operative day, his negative nitrogen balance then decreased and was only 1.4 gm. on the thirteenth post-operative day. During the remaining three days of the experiment the negative nitrogen balance again increased probably due to a small pressure area occasioned by his cast. The phosphorus balance only roughly paralleled the nitrogen balance. There was an unexplained positive phosphorus balance during the control days, and throughout the experiment the phosphorus balance tended to be less negative than one would have expected from the nitrogen balance.

One of the most striking findings was the failure of the calcium balance to become markedly negative after the operation. Moreover, the urinary calcium almost exactly equalled the calcium intake (331 mg.). Ordinarily the calcium content of the feces on a low calcium intake is much greater than the intake. In this case, since there were virtually no feces (*vide infra*), all of the calcium apparently was excreted in the urine.

Perhaps one of the most interesting aspects of this case was the lack of fecal excretion after the first few days. This is reminiscent of the "fasting man" of Benedict (1915) who fasted 31 days and had no fecal excretions after the first few days. This study brings up the feasibility of feeding a patient 100 per cent by vein. We suspect that 100 per cent intravenous feeding is very different from 95 per cent intravenous feeding. It would appear from the absence of fecal excretions that the gastro-intestinal tract must have been at complete rest. Feeding 100 per cent by vein may constitute a means of therapy in such conditions as gunshot wounds of the abdomen, colitis, intestinal obstruction, ruptured gut, *et cetera*.

In Fig. 91 it will be seen that the 17-ketosteroid excretion remained practically constant through and including the first day after the operation, after which there was a marked fall. This is strong evidence that the fall after operation which we have emphasized elsewhere [Forbes, Donaldson, Reifenstein, and Albright (1947)] is not due to a decreased food intake such as usually occurs after an operation.

(II) *Osteoporosis of acromegaly*

Although from a clinical point of view demineralization is not an important feature of acromegaly, there is considerable evidence that this condition is associated with a loss of calcium probably on an osteoporotic basis. Bauer and Aub (1941) using a neutral, low-calcium rather low-nitrogen diet (*circa* 10 gm per day) studied the calcium metabolism of 5 acromegalic patients. Four of the five patients excreted much more calcium in the urine than normal. The fecal calcium excretions were normal. Furthermore the four patients who had hypercalcaemia were in negative nitrogen balance while the patient who did not have hypercalcaemia was in positive nitrogen balance, what is more the patient who had the most hypercalcaemia was in the greatest negative nitrogen balance. We have data on two cases of acromegaly [Case No 17 (Metabolic Study No 10) and Case No 18 (Metabolic Study No 11)] both of whom received a high nitrogen intake. Both of these patients had markedly negative calcium balances in spite of nitrogen equilibrium. The serum calcium, phosphorus, and phosphatase values in acromegaly are consistent with an osteoporosis and inconsistent with almost any other metabolic bone disease. Thus the serum calcium and phosphatase values are normal and the serum phosphorus level usually definitely high (*circa* 4.5 to 5.5 mg per cent) even higher than in the post-menopausal state. The average serum phosphorus value of 14 acromegalic patients reported by Reifenstein, Kinsell and Albright (1946) was 4.33 mg per cent as compared with 3.75 and 3.21 mg per cent the average values for 42 cases of post-menopausal osteoporosis and for normal individuals respectively. All of the differences are significant statistically.

As a cause for the demineralization of bone in acromegaly, five possibilities come up for consideration.

(1) There are those who attribute the demineralization to an accompanying hyperparathyroidism. For a discussion of this aspect, see Perlman (1944). The argument rests mostly on the fact that hyperplasia of the parathyroids and even parathyroid adenomas commonly accompany eosinophilic tumors of the pituitary. However almost all organs are hypertrophied in acromegaly, so hyperplasia in itself argues more for a compensatory increased production as opposed to an overproduction. Against the demineralization being due to a hyperparathyroidism are the absence of a high serum phosphatase level, the elevation rather than a lowering of the serum inorganic phosphorus level [Reifenstein, Kinsell and Albright (1946)] and the absence of a hypercalcaemia. Thus does not mean that hyperparathyroidism due to a parathyroid adenoma may not be a relatively frequent complication of acromegaly, because of the tendency for adenomata to develop in hyperplastic tissue, indeed, in our clinic we have a

patient with kidney stones and acromegaly who has a high serum calcium, a normal rather than a high serum phosphorus and marked hypercalcaemia.

(2) The second possible explanation of the demineralization in acromegaly is that eosinophilic tumors of the pituitary may produce an excess of the corticotrophic hormone and thus lead to an overproduction of the 'Sugar' or 'S' hormone and that this in turn may lead to an osteoporosis (see discussion on Osteoporosis of Cushing's Syndrome p 165). The hyperplasia of the adrenal cortex which accompanies acromegaly might support this hypothesis especially since the 17 ketosteroid excretion is not elevated in acromegaly [Fraser Forbes Albright Sulkowitch and Reifstein (1941)] so that the hyperplasia is not due to an overproduction of the 17 ketosteroid precursors of the adrenal cortex (see p 167). The fact that the 'S' hormone inhibits the growth hormone (see p 166) does not preclude its overproduction in acromegaly since in that condition there may be too much growth hormone to be entirely inhibited. The problem should be settled easily by the determination of the 11 oxycorticosteroid (see page 158) and cortin excretions in the urine. These studies are in progress.

(3) The third possible explanation for osteoporosis in acromegaly is that eosinophilic tumors of the pituitary may produce an excess of the thyrotrophic hormone and thus lead to an overproduction of the thyroid hormone and that this in turn may lead to an osteoporosis (see discussion on the relation of thyrotoxicosis to osteoporosis p 149). The hyperplasia of the thyroid which occurs in acromegaly might support this hypothesis especially since Davidoff (1926) found the metabolic rate elevated in all of 70 cases. Subsequently however Cushing and Davidoff (1927b) pointed out that the increase in the metabolic rate persisted after thyroidectomy and hence was probably not due to the thyroid. This observation together with the lack of other manifestations of thyrotoxicosis in most patients with acromegaly, renders less plausible the assumption that there is an overproduction of thyroid hormone in these patients and that this is the cause of the osteoporosis.

(4) A fourth possibility is that the increased protoplasmic mass in acromegaly (see enlargement of all organs) requires a higher nitrogen intake to keep in nitrogen balance. Hence the likelihood of an inadequate nitrogen intake is increased. This favors the possibility of there being too little material for the osteoblasts with which to build bone matrix which in turn might result in osteoporosis (see discussion on Osteoporosis from Malnutrition p 148). In other words there is a demand for amino acids by all tissues and the bone matrix loses out because of a low priority rating. The normal serum phosphatase level favors osteoporosis. This explanation is in agreement with the finding of Bruer and Aub (1941) mentioned

above of a relationship between the calcium and the nitrogen balances in patients with this disorder

(5) The fifth and most obvious possibility is to relate the bone disorder to the hypogonadism which accompanies most cases of acromegaly in other words to liken it to the osteoporosis encountered in the post menopausal state. If this is the correct explanation, the condition should respond to estrogen therapy, it does. Metabolic studies were carried out on two cases to determine the effect of estrogen therapy. In each case the negative calcium balance was turned into a positive one, the serum phosphorus level was lowered and in one case the serum phosphatase level was elevated (see Metabolic Studies No 10 and 11). One of the two cases (Case No 17) had a definite reduction in the size of the hands with estrogen therapy, and most cases of acromegaly are clinically benefited by the estrogenic medication. This explanation runs into difficulty however, in men who have no apparent gonadal deficiency. For example Case No 18 (see Metabolic Study No 11) who had a normal follicle stimulating hormone excretion and normal findings on testicular biopsy had a markedly negative calcium balance which became strongly positive with estrogen therapy. All in all, however, the authors rather favor the fifth hypothesis.

Metabolic Study No 10

Case No 17 Acromegaly Amenorrhea, Estradiol Dipropionate, Diethylstilbestrol and Progesterone Therapy

C S (M G H 347319) an 18 year old girl had her first catamenia at 14 years. At 16 two years before admission she became amenorrheic and started to grow at an accelerated rate. One year before admission she developed chronic fatigue, an excessive appetite, a weight gain of 20 pounds, puffiness of the hands and feet and around the eyes, numbness of the hands and forearms and an increase in the hair on the face, arms and legs but no change in the hair of the head. Her voice which had always been low, did not change. Mild acne had been present on the face for four years. There were no headaches and no gastrointestinal or visual symptoms.

Physical examination showed a tall (69 in.) well nourished (180 pounds) girl.

Fig 9a Effect of Estradiol Benzoate Therapy (Patients B and C) as Compared with No Hormone Therapy (Patient A) on the Calcium Balances in Patients with Osteoporotic Process due to Operation and Immobilization

For explanation of construction of chart see Appendix page 309

All three patients were active healthy adults before operation. Note the increased calcium excretion, mostly urinary, after the operation in patients (B) and (C) compared with before the operation in patient (A). Note the decreased calcium excretion in patients (B) and (C) under estradiol benzoate therapy whereas the increased calcium excretion persisted in patient (A) who did not receive hormone therapy. [From Reifenstein and Albright (1947) and Albright (1947a)]

with a square muscular build, a prominent jaw, large, pale, puffy hands, and hirsutism of legs, arms, abdomen, and face. There was mild acne on the forehead. Examination of the fundi and the visual fields was not remarkable. The teeth were not separated, the thyroid gland was not enlarged. The larynx was moderately large, the breasts well developed, the clitoris not enlarged, and the pelvic organs not abnormal. Blood pressure was 110/70. The remainder of the examination was not unusual. X rays of the skull revealed no enlargement of the sella, films of the hands showed no tufting of the terminal phalanges, x rays of the spine showed decreased density of bones with multiple herniations of nuclei pulposi into the lumbar and thoracic vertebrae, with anterior wedging of the first and second lumbar vertebrae, and with slight thoracic kyphosis, there was no increase in the antero-posterior diameters of the vertebrae. Laboratory studies: serum calcium 10.9 mg per 100 cc, serum phosphorus 3.9 mg per 100 cc, serum alkaline phosphatase 4.0 Bodansky units, serum total protein 6.4 gm per 100 cc, serum sodium 139.5 m eq per liter, serum potassium 4.8 m eq per liter, serum chloride 108 m eq per liter, serum carbon dioxide content 27.7 m eq per liter, serum cholesterol 203 mg per 100 cc, glucose tolerance test normal, insulin tolerance test—insulin resistant, basal metabolic rate plus 15, follicle stimulating hormone in urine—negative for 6.5 mouse units per 24 hours (low), 17 ketosteroid excretion in urine 17.7 mg per 24 hours (normal), "11 oxy steroid" excretion in urine 0.16 to 0.30 mg per 24 hours (normal), and urinary corticosteroid excretion by biological assay—positive for 3 and negative for 6 mouse units per 24 hours (normal). This case was mentioned in a previous communication [Reifenstein, Kinsell, and Albright (1946)].

The metabolic data of Case No. 17 are shown in Fig. 96. The study, conducted in six day stool periods, consisted of (1) six control periods, (2) 27 days with estradiol dipropionate 5 mg intramuscularly each day at home, (3) transphenoidal removal of part of the pituitary gland, (4) 164 days without therapy at home, (5) 30 days with diethylstilbestrol 1 mg by mouth daily at home, (6) 94 days with diethylstilbestrol 15 mg by mouth daily at home during which progesterone 25 mg intramuscularly daily for five days was given on two occasions approximately 8 weeks apart, and (7) six periods with diethylstilbestrol 15 mg by mouth daily.

The data in Fig. 96 are self-explanatory. Attention should be called to (1) nitrogen and phosphorus equilibria during the control periods (1-6), (2) the negative calcium balance during the control periods, (3) the marked shift in the calcium balance to retention without a significant change in the nitrogen balance with diethylstilbestrol therapy, (4) the tendency of the phosphorus balance to go along with the calcium balance during the estrogen therapy, (5) the high serum phosphorus level during the control periods, (6) the marked fall in the serum phosphorus level during therapy with both types of estrogen (estradiol dipropionate and diethylstilbestrol), (7) the lack of effect of partial pituitaryectomy on the elevated serum phosphorus level, (8) the failure of the serum alkaline phosphatase level to rise with the estrogen therapy, and (9) the high normal level of 17 ketosteroid excretion during the control periods and its reduction with estrogen therapy.

Metabolic Study No. 11

Case No. 18. Acromegaly, Estradiol Dipropionate Therapy

C. O. R. (M. G. H. 380940), an 18-year-old boy, began puberty at the age of 14. His growth from the age of 15 to the time of admission was 5 inches. During the

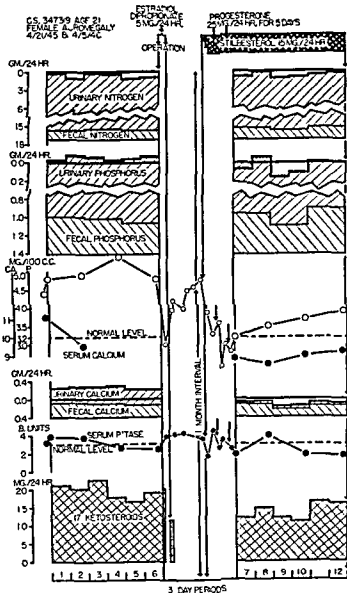


Fig 96 Metabolic Study of Effect of Estradiol Dipropionate Diethylstilbestrol and Progesterone Therapy on a Female Patient (C S, M G H 347319) with Acromegaly, Case No. 17

For explanation of construction of chart see Appendix page 300

Note the nitrogen and phosphorus equilibria during the control periods the marked retention of calcium and phosphorus but not nitrogen with diethylstilbestrol therapy, the high serum phosphorus level during the control periods, the marked fall in the serum phosphorus level with estrogen therapy, the lack of effect of partial pituitaryectomy on the serum phosphorus level the failure of estrogen therapy to influence the serum phosphatase level and the high normal level of 17 ketosteroid excretion during the control period which fell with estrogen therapy [From Reifenstein, Kinsell, and Albright (1946)]

same interval he gained 50 pounds in weight and developed unusually large hands, feet, and head. About two years before admission he began to notice excessive fatigue and somnolence, pain referred to the spine when he was tired, recurrent frontal headaches which increased in frequency and severity, lacrimation and photophobia, and pain in the maxillae. For one year before admission he had occasional attacks of epigastric pain, nausea, and vomiting. At the time of admission he had a deep voice, shaved daily, and had occasional erections but no emissions.

On physical examination the patient was a tall (73 in.), moderately well nourished (168 pounds) boy with large, beefy hands and feet. Hair distribution was normal for an adult male. Examination of the visual fields and the fundi was not unusual. The teeth were not separated, the thyroid gland was not enlarged. There was dorsal kyphosis, lumbar lordosis, and right scoliosis. The breasts were flat and the external genitalia and the prostate were normal. The skin was moist with acne vulgaris on the face. The blood pressure was 110/75. The remainder of the examination was not remarkable. A ray examination of the skull showed that the pituitary fossa was enlarged anteriorly and downward with the floor of the fossa projecting into the left sphenoid sinus, the left posterior clinoid was partially eroded, x rays of the hands showed no tufting of the terminal phalanges, films of the spine showed scoliosis and slight "epiphysitis" of the vertebrae but no anterior overgrowth of the vertebrae (see p 196), x ray examination of the gastro intestinal tract revealed no pathology. The testis on biopsy was normal and the sections revealed spermatogenesis progressing normally in the tubules with the formation of normal sperm in moderate numbers, many lumina with desquamated spermatocytes, and Leydig cells that were normal in quantity and quality and contained their usual inclusion bodies.

Laboratory studies. Sulkowitch test on the urine was 3 plus serum calcium 10.8 mg. per 100 cc., serum phosphorus 6.3 mg. per 100 cc., serum alkaline phosphatase 3.3 Bodansky units, serum total protein 6.6 gm. per 100 cc. with an albumin/globulin ratio of 2.0, serum chloride 105 m eq. per liter, serum carbon dioxide content 23 m eq. per liter, serum cholesterol 162 mg. per 100 cc., fasting blood sugar 91 mg. per 100 cc., basal metabolic rate from minus 10 to plus 6, follicle stimulating hormone test positive for 26 and negative for 52 mouse units per 24 hours (normal), and 17 ketosteroid excretion of 12.2 mg. per 24 hours (normal). This case was mentioned in a previous communication [Reifenstein, Kinsell, and Albright (1946)].

The metabolic data of Case No. 18 are shown in Fig. 97. The study, conducted in six day periods, consisted of (1) four control periods, (2) four periods with estradiol dipropionate 5 mg. intramuscularly every three days, (3) three periods with estradiol dipropionate 10 mg. intramuscularly daily, and (4) four control periods without medication during the last two of which there was a moderate decrease in intake of nitrogen, phosphorus, and calcium.

The data in Fig. 97 are self explanatory. To be noted are (1) the moderately positive nitrogen balance throughout which was not affected by estrogen therapy, (2) the very negative calcium and phosphorus balances in the control periods (1-4), (3) the marked retention of calcium and phosphorus with estrogen therapy which increased with time and persisted for at least 24 days after the therapy was discontinued, (4) the fact that the decrease was in the fecal as well as the urinary calcium excretion during the estrogen therapy, (5) the high serum phosphorus

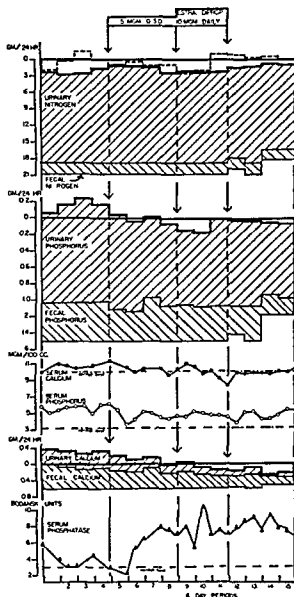


Fig 97 Metabolic Study of Effect of Estriadiol Dipropionate Therapy on a Male Patient (C O R, M G II 350940) with Acromegaly, Case No 18

For explanation of construction of chart see Appendix, page 309

Note the moderately positive nitrogen balance uninfluenced by therapy, the very negative calcium and phosphorus balances in the control periods the marked retention of calcium and phosphorus with estrogen therapy, the high serum phosphorus level in the control periods which tended to fall with therapy, the rise in the serum phosphatase level with estrogen therapy, and the lack of significant change in the serum calcium level [From Reifenstein, Kinsell, and Albright (1916)]

level during the control periods (6) the tendency of the serum phosphorus level to fall with estrogen therapy, (7) the rise in the serum alkaline phosphatase level with estrogen therapy, and (8) the failure of the serum calcium level to change significantly during the estrogen therapy

A word needs to be said about the vertebral changes in acromegaly. After closure of the epiphyses, there is still a possibility for restricted endochondral bone formation at certain sites. Erdheim (1931) showed in a

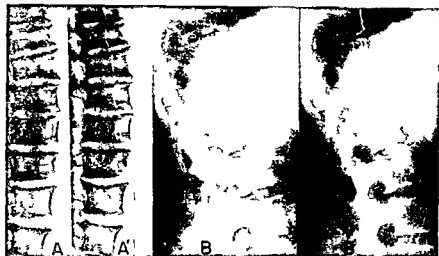


Fig 98 X ray Films Showing Vertebral Changes in Acromegaly

(A) X ray film of spine taken at post mortem [From Erdheim (1931)], (B) x ray film of spine taken *in vivo* (A. P. M. G. H. 135659), (A') and (B') same as (A) and (B) except that white lines have been drawn in to separate the new growths from the original vertebrae. Note that in both Erdheim's case and the authors the maximum changes occur at about the level of the ninth thoracic vertebra. Note, as Erdheim pointed out, that the vertebrae, in contrast to the usual rule, decrease in size from above down, note in (A') and (B) that this decrease is due to a decrease in the new bone formation. [From Albright (1947a)]

most thorough post mortem study, and we can confirm his findings by x ray studies (see Fig 98), that the cartilaginous end plates of the vertebrae in acromegaly again start producing endochondral bone which together with increased periosteal bone formation accounts for the increased width of the vertebrae in the antero-posterior diameters (see Fig 98 and 99). For a discussion of the vertebral changes in acromegaly in the English language see Wayne, Bennett, and Bauer (1945)

(I) *Idiopathic Osteoporosis*

Under the diagnosis of idiopathic osteoporosis the authors group those rare cases where the clinical manifestations are similar to those in post menopausal or senile osteoporosis but where the individual is not post menopausal or senile. We have studied four such patients [Albright, Reifenstein, and Forbes (1944, 1946)] a man of 28 who developed severe osteoporosis of the spine during a period of three years following an automobile accident in which the spine itself was not injured a 24 year old single college girl whose history is reviewed below (Metabolic Study No 12) and two young married women (Metabolic Study No 13 and another case) in both of whom the osteoporosis was made worse by pregnancy.



Fig 99 Photograph of Vertebra from a Patient with Acromegaly to Show New Bone Formation

Note that new bone formation is greatest on the anterior surface and least on the lateral surfaces. This explains why an acromegalic patient often can bend freely sideways but not frontward. [From Erdheim (1931), and Albright (1947a).]

The cause of the osteoporosis remains obscure. In view of the marked osteoporosis in dogs following gastrectomy [Bussabarger, Freeman, and Ivy (1938)] alterations in gastric function were looked for (see Cases No 19 and 20). Nothing very incriminating was found. From calcium balance studies on three of the above mentioned four patients, it was ascertained that the malady is not benefited by vitamins A, C, and D, testosterone propionate*, diethylstilbestrol, estradiol dipropionate, or sodium fluoride. A high protein intake was of moderate benefit in two instances; serum albumin intravenously apparently benefited one patient who later failed to respond to the same therapy by mouth (see Fig 103). Therapeutic abortion markedly improved the calcium balance in one patient (see Fig 102).

* Testosterone propionate was tried only on the male patient, on theoretical grounds it would be more apt to have a beneficial effect in female patients.

The following two cases are of interest

Metabolic Study No 12

Case No 19 Idiopathic Osteoporosis

D B (M G H 452389), a 24 year old single Californian college girl, first noticed pain in her arches three years before admission. The pain spread to other parts of her skeleton, she lost about two inches in height and developed a curvature of the spine. For five years she had noticed brittle fingernails and increased curliness of her hair. The menarche had started at 14, her periods were regular.

X rays showed marked demineralization, especially of the spine and the classic codfish type of vertebral deformity, the lamina dura was normal. The serum calcium, phosphorus, and phosphatase values were normal, the urinary calcium excretion was high (*circa* 160 mg daily). There were a few findings to suggest gastro intestinal insufficiency: the vitamin A level was low normal (0.5 units per cc), the intestinal rate was somewhat rapid, the mucosal pattern of the small bowel suggested "vitamin deficiency", the hemoglobin was slightly low, and the glucose tolerance test showed a "flat curve". On the other hand, the gastric acidity was normal, the serum protein was only slightly decreased (6.5 gm per 100 cc), the level of serum carotinoids was normal, there was no increase of fat in the stools.

She was studied for 29 three-day metabolic periods. Periods 1 through 22 are shown in Fig 100, periods 17 through 39 are shown in Fig 101. To be noted in Fig 100 are (a) during the control periods 1 through 6, the urinary calcium was moderately high and she was in negative calcium balance, (b) during the administration of estradiol dipropionate, 5 mg every other day (periods 7 through 16), there was very little if any change, as was to be expected since her catamenia was normal, and, finally, (c) with the administration of 100,000 units of vitamin D daily (periods 17 through 22), there was no change in her calcium balance, merely a fall in the fecal calcium excretion and a rise in the urinary calcium excretion. This absence of effect with vitamin D was also as expected since her osseous malady is osteoporosis, not osteomalacia. The problem is not to calcify matrix but to grow matrix. This experiment supports our contention that calcium *per se* is not a stimulus to bone formation.

During periods 23 through 33 (see Fig 101), she received 350 gm of casein hydrolysate (Amigen) daily by stomach tube, plus liver extract, stomach extract, and "all the vitamins" (alpha tocopherol, ascorbic acid, and vitamins B, K, and A). On this regimen there was a positive nitrogen balance but the calcium balance remained essentially unchanged. At the end of this high nitrogen regimen the glucose tolerance test and the mucosal pattern of the bowels by x ray were less abnormal. However, the final 6 control periods (34 through 39) showed no improvement in the calcium balance over periods 17 through 22.

Metabolic Study No 13

Case No 20 Idiopathic Osteoporosis, Pregnancy

E L (M G H 389504), a 30 year old housewife, was first seen in 1943 for osteoporosis. She had had slight bone pain in 1938 which had become severe

during her first pregnancy in 1939 and had culminated in a back injury at the time of delivery. Not long afterward she had fractured a femur

On admission, she showed the deformities, the x ray findings, and the normal

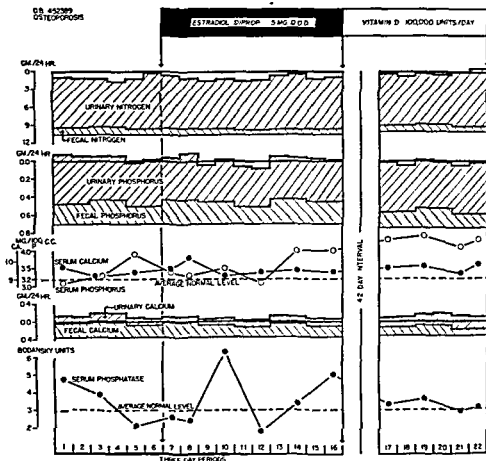


Fig 100 Metabolic Study on the Effect of Estradiol Dipropionate and Vitamin D Therapy on a Female Patient (D B, M G II 452389) with Idiopathic Osteoporosis, Case No. 19

For explanation of construction of chart see Appendix, page 309

Note that urinary calcium excretion was high during the control periods when she was in a negative calcium balance, and that neither estradiol dipropionate nor vitamin D therapy significantly reduced the negative calcium balance, although there was a shift of calcium from the feces to the urine with the latter medication [From Albright, Reifenstein, and Forbes (1916)]

blood chemistry (serum calcium, phosphorus*, and phosphatase) of advanced post menopausal or senile osteoporosis in spite of her youth and good health

* To be strictly accurate, the serum phosphorus level was moderately high as is so often the case in post menopausal osteoporosis (see p 145)

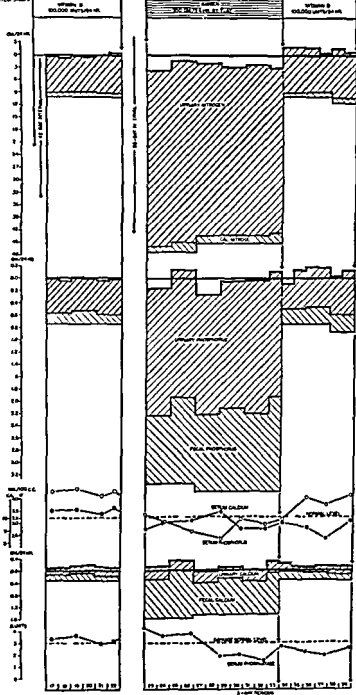


Fig 101 Continuation of Metabolic Study on Patient with Idiopathic Osteoporosis (cf Fig 100), Effect of High Protein Intake

For explanation of construction of chart see Appendix, page 309

Note that a high protein intake in the form of casein hydrolysate (Amigen) (350 grams daily by stomach tube), supplemented with liver extract, stomach extract, alpha tocopherol, ascorbic acid, and vitamins B₁₂ and A, induced a positive nitrogen balance but failed to induce a significant retention of calcium. Note also the fall in the serum phosphorus values during this regimen. (From Albright, Reifenstein, and Forbea (1946)).

otherwise. At the onset of the studies (December 14, 1944), she was in her second pregnancy, her last period having been in July 1944. Her osteoporosis had already become much worse. It was decided to carry out metabolic studies before and after interruption of her pregnancy.

The metabolic findings are shown in Fig. 102 and 103. It will be noted in Fig. 102 that, during the four 3 day metabolic periods before interruption of pregnancy (periods 1 through 4), her serum protein level was low (a normal finding in pregnancy) and she was in markedly negative calcium balance. When she was put on the same regimen after interruption of the pregnancy (periods 5 through 10), the serum protein was considerably higher and the calcium excretion was considerably decreased, although she was still in negative balance.

There were some findings to suggest that the osteoporosis might be secondary to a gastrointestinal inadequacy. Thus her serum protein and hemoglobin were slightly low, gastric analysis showed no free acid. Since a low serum protein level is found in several conditions associated with osteoporosis (old age, Cushing's syndrome, nephrosis, malnutrition) the effect of the administration of large amounts of plasma protein was studied. She was given 500 cc. of plasma intravenously daily for 12 days (periods 11 through 14). The experiment was complicated by the fact that she developed a high temperature (? upper respiratory infection, ? toxic reaction) during the second half of these 12 days (periods 13 and 14). However, during the first 6 days there was already a marked rise in her serum protein level and she went into positive calcium balance for the first time (see Fig. 102). With the fever there was the expected reversal in the calcium, phosphorus, nitrogen and potassium balances (see Fig. 102) but the 17-ketosteroid and '11-oxysteroid' (see p. 153) excretions remained unaltered! Was the failure of the two steroid excretions to vary connected with the fact that she was furnished with plasma protein to burn and did not need to mobilize her own body protein?

Shown also in Fig. 102 are six 3 day control periods following the administration of the plasma (periods 15 through 20), six 3 day periods on a low nitrogen intake (periods 21 through 26) and, finally, six 3 day periods on a high nitrogen diet (periods 27 through 32). Note that the patient again showed a decidedly positive calcium balance when the serum protein for the second time reached normal during periods 31 and 32. Other points of possible interest are the high serum phosphorus level throughout, the fall in 17-ketosteroid excretion during the low nitrogen intake, and the rise in 11-oxysteroid excretion on the high nitrogen intake.

It was decided to repeat the experiment with plasma protein (see Fig. 103). Accordingly she was brought back to the ward and studied for eight 3-day control periods. During the first two of these she received the same low calcium diet that she had received during periods 1 through 26. During the remaining six 3 day control periods (periods 35 through 40) she received a somewhat higher calcium intake on which regimen she was almost in calcium balance. During periods 41 through 44 she received purified plasma albumin which resulted in a rise in the serum protein level, a fall in the calcium excretion and a positive calcium balance. The positive calcium balance continued for eight 3-day control periods following cessation of the albumin injections (periods 45 through 52), and then failed. In a later experiment serum albumin was given by mouth instead of intravenously for 12 days without beneficial effect on the calcium balance.

Fig. 103 shows in addition negative results with two other therapeutic agents,

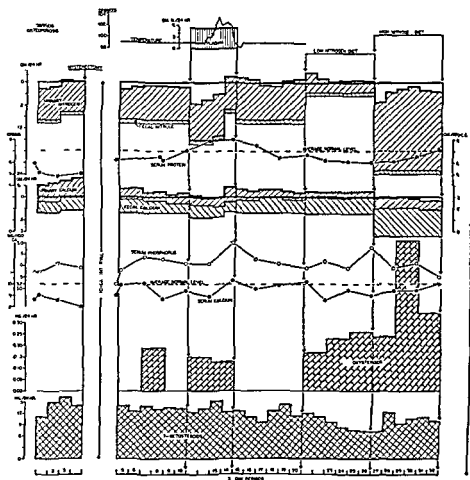


Fig 10² Metabolic Study of Effect of Interruption of Pregnancy, of Plasma Administration by Vein of Low and High Protein Diets and of Fever on a Female Patient (E. L. M. G. H. 38904) with Idiopathic Osteoporosis, Case No. 20

For explanation of construction of chart see Appendix page 309

Note that the calcium balance was markedly negative while the pregnancy lasted that it improved when the pregnancy was interrupted (see periods 5 through 10), that it became positive for the first time during plasma administration (see periods 11 through 13) that it again became negative when the patient developed a fever (see period 14) and finally that it once more became positive on a very high protein diet (see periods 27 through 32). Note especially that the calcium balance was most negative when the serum protein level was lowest (periods 1 through 4) and that the calcium balance was positive on the two occasions when the serum protein level was normal (period 13 and period 32). [From Albright, Reifenstein, and Forbes (1946)]

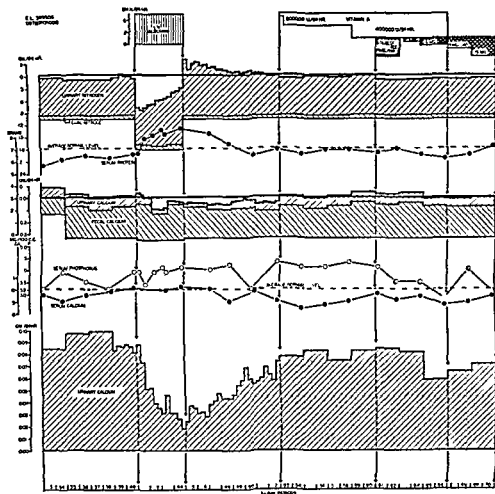


Fig 103 Continuation of Metabolic Study on Patient with Idiopathic Osteoporosis (cf Fig 102), Effect of Albumin Administration Intravenously, of Vitamin A Therapy, and of Diethylstilbestrol Therapy

For explanation of construction of chart, see Appendix, page 309 At bottom of the figure the urinary calcium excretion is charted separately on a scale magnified ten times

Note that the administration of purified albumin intravenously resulted in a rise in the serum protein level, as might be expected, this rise in the serum protein was dependent on a rise in the serum albumin level Note especially that the rise and fall in the serum protein level is attended by a fall and rise in the urinary calcium excretion Finally, note that large doses of vitamin A and of diethylstilbestrol had no significant effect on the calcium balances although the latter medication caused a fall in the serum phosphorus level (From Albright, Reifenstein, and Forbes (1946)]

vitamin A and diethylstilbestrol. The former was tried because of the studies of Dr. S. Burt Wolbach (1946) on the effect of vitamin A on the skeleton. It will be noted that doses up to 400,000 units a day were without effect (see periods 53 through 60). Massive doses of diethylstilbestrol up to 15 mg. daily, likewise had little or no effect although there was some tendency for the serum phosphorus level to decrease with the administration of this drug (see periods 61 through 70).

It is seen, therefore, that the studies discussed under Fig. 102 and 103 support the possibility that serum albumin is the precursor of bone matrix. For further discussion of this aspect of osteoporosis see Forbes, Albright, Reinkenstein, Bryant, Cox, and Dempsey (1947), and Albright (1947c).

CHAPTER 7

METABOLIC BONE DISEASE OSTEOMALACIA*

I DEFINITION AND NATURE OF OSTEOMALACIA

Osteomalacia ('adult rickets') is a disorder of bone tissue characterized by a failure of calcium salts to be deposited promptly in the newly formed bone matrix (osteoid). The reason for this failure is to be found in the body fluids which contain too little calcium for the level of inorganic phosphorus, or to place the emphasis differently, too little inorganic phosphorus for the level of calcium to allow for normal precipitation of whatever salt of calcium it is that is precipitated into bone matrix. The serum calcium level is normal or low, the serum phosphorus† level is low or normal, in any case the product of the serum calcium in milligrams and the serum phosphorus in milligrams is lower than normal. Furthermore the failure of the bone to be calcified (or phosphorized) leads to weakened bones: this leads to an increased activity of the osteoblasts: this in turn leads to a high serum alkaline phosphatase level. Rickets has all the characteristics of osteomalacia plus some additional changes at the growing epiphyseal cartilage, notably faulty calcification of the zone of provisional calcification.

With respect to the serum calcium and phosphorus findings it is possible to divide cases of osteomalacia into three types: (a) those in which compensatory over activity of the parathyroids is lacking; (b) those where there is compensatory over activity of the parathyroids sufficient to maintain the serum calcium at a normal level; and (c) those where there is compensatory over activity of the parathyroids but where this is insufficient to maintain the serum calcium at a normal level. In the first type the serum calcium would be low and the serum phosphorus normal; in the second the serum calcium would be normal and the serum phosphorus low; and in the third both the serum calcium and the serum phosphorus would be low.

II DIFFERENTIATION OF OSTEOMALACIA FROM OSTEOPOROSIS AND OSTITIS FIBROSA GENERALISATA

(A) *Differential Diagnosis*

The differential diagnosis has been discussed in the chapter on the general considerations of metabolic bone disease (see Chapter 5, p. 111).

* In this section the authors have drawn freely from All right Burnett Parson, Reifenslein and Roos (1946).

† In this chapter as in other sections of this work by serum phosphorus is meant serum inorganic phosphorus.

The expected findings in osteomalacia are a normal or low serum calcium, a low or normal serum phosphorus (most commonly a normal serum calcium with a low serum phosphorus), and a high serum alkaline phosphatase level, in contrast to these findings are the normal serum calcium phosphorus, and phosphatase levels in osteoporosis and the high serum calcium low serum phosphorus and high serum phosphatase levels in osteitis fibrosa generalisata when the latter is due to hyperparathyroidism

(B) *Body Fluid Unsaturation and Bone Resorption*

Why in osteomalacia, where the body fluids are apparently so unsaturated with respect to calcium phosphate, are not calcium ions and phosphate ions resorbed rapidly from the bones so that saturation of the body fluids is re-established? This question is all the more pertinent since in osteitis fibrosa generalisata the bones continue to give up calcium to the bitter end. A possible explanation may be that in osteomalacia all the trabeculae become covered with osteoid tissue which insulates the calcified matrix from the body fluids (see Fig 129, p 256). The reader may then ask "Why do not the trabeculae in osteitis fibrosa generalisata become insulated with osteoid?" The authors do not have even a poor answer to this question

III MILKMAN'S SYNDROME

(A) *Is Milkman's Syndrome a Form of Osteomalacia?*

Milkman's classical case (1930, 1934) was that of a woman of forty three with a past history of the passing renal calculi, whose first symptoms were pain in the lower back and extremities and a waddling gait. No skeletal abnormalities were recognized by x ray during the first two years of her illness thereafter 'ribbon like zones' of decalcification, many of them symmetrical, appeared. The patient died after six years of generalized pains. By that time 13 bony defects were present but the skull and pelvis remained uninvolved. Of interest among the autopsy findings were "diffuse nephritis" and the diagnosis of osteomalacia by two of three pathologists. Milkman emphasized the absence of bone deformities and the late occurrence of bone displacement, and defined the syndrome as a "systemic disease involving the entire skeleton, flat and tubular bones, with symmetrical fractures starting the cortex". Not emphasized by Milkman and possibly of importance in view of the discussion to come concerning renal acidosis (see p 227) and the Fanconi syndrome (see p 257) were the diffuse nephritis, the history of passing stones, and the finding of intermittent but rather marked glycosuria (up to 5 per cent) and ketonuria in the presence of normal fasting blood sugar levels.

The first question is are the findings in Milkman's syndrome due to osteomalacia? The authors feel certain that they are. This conclusion is based on four considerations (a) the symmetrical ribbon like zones of decalcification seen by x ray and often occurring in otherwise normal appearing bone, are characteristic of osteomalacia and of that disease alone (b) the serum calcium phosphorus and phosphatase findings in most of the undoubted cases are those of osteomalacia (c) such patients respond to therapy based on the assumption that they have osteomalacia and (d) the histopathology, if carefully studied is that of osteomalacia. These items will now be discussed one by one.

The formation of bone consists of two steps laying down of the matrix by the osteoblasts and the calcification of the matrix. In osteomalacia the first of these steps is intact the second deficient. The healing of a fracture consists of the same two steps. In a fracture complicating osteomalacia one would anticipate that the first step would proceed normally or even better than normally in view of the increased number of osteoblasts whereas the second step would be faulty. Such has been shown to be the case in experimental osteomalacia in rats. Ham Tisdall and Drake (1938) did a very simple and conclusive experiment on rats. Fractures were produced in a group of rachitic rats x rays at the end of three weeks gave the impression that no union had taken place histological studies however, showed the presence of excellent calluses which were not calcified. Similarly treated animals allowed to live four days longer and given vitamin D showed rapid calcification of the calluses but little change in their histological appearance. Thus if a fracture without displacement were to occur in a patient with osteomalacia one would expect union to occur but the zone of callus formation to remain uncalcified.

But do such fractures occur in undoubted cases of osteomalacia in humans? The answer is yes. The subject has been extensively discussed in the German literature notably by Looser (1920) who characterized such united but uncalcified fractures as Umbauzonen (zones of transformation). To be sure it was not Looser's conception that the first step was an actual fracture he conceived of the process as a slowly progressing callus formation inside the bone brought about by a mechanical irritation due to strain and by small local infractions. The net result is a local transformation of bone. By transformation (Umbau) of bone he meant a change from lamellar bone to that characteristic of a callus namely braided (geflechtartig) bone. This author goes on to state that since the callus in osteomalacia remains uncalcified for a long time it is understandable why the zone of bony transformation remains for a long time after its formation as a zone of decreased density by x ray.

From the above discussion it seems clear that the ribbon like zones of

decalcification characteristic of Milkman's syndrome are consistent with an underlying osteomalacia. The question arises as to whether they are found in any other systemic bone disease. It is the authors' opinion that they are not. The present authors agree that lesions occur in conditions other than osteomalacia which by x-ray somewhat resemble these



Fig 101 X-Ray Films of Right Tibia on Patient A. K. (M. G. H. 26700) with Polyostotic Fibrous Dysplasia (Osteitis Fibrosa Disseminata) to Illustrate Similarity in X-Ray Appearance of Pseudarthrosis (Arrows) with Pseudofractures of Milkman (See Fig 105, 106, 108 and 109)

(A) on 11-28-38, (B) on 2-2-44 [From Albright, Burnett, Parson, Reifenstein, and Roos (1916)]

united but uncalcified fractures seen in osteomalacia. This is especially true in Paget's disease, polyostotic fibrous dysplasia (osteitis fibrosa disseminata), and osteogenesis imperfecta. For example, in polyostotic fibrous dysplasia at a point where marked bending has occurred, one often sees by x-ray a somewhat similar appearance (see Fig 104), it is quite clear, however, that such a lesion represents a fibrous and cartilaginous union,

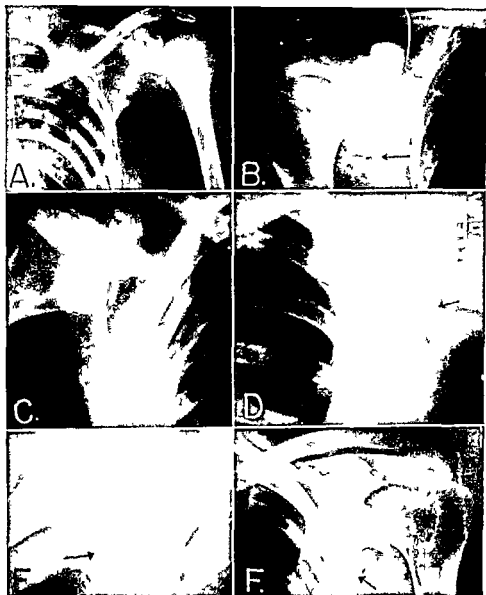


Fig. 10. X Ray Films of Six Different Scapulae to Emphasize Frequency and Uniformity of Appearance of Pseudofractures (See Arrows) in the Scapulae

(A) Milkman's case (1934) (B) case of Camp and McCullough (1941) (C) Case No. 21 right scapula (D) Case No. 21 left scapula (E) Case No. 22 and (F) Case No. 23. The authors are indebted to Dr. Milkman and the Journal of Roentgenology and Dr. Camp and Radiology for permission to use Fig. 10A and Fig. 10B respectively [From Albright, Burnett, Larson, Reifenstein and Roos (1946)]

really a pseudarthrosis, not an uncalcified callus. Furthermore, the fracture-like appearances in most of these other conditions always occur through

areas of definite bone pathology by x ray (see Fig 104), in osteomalacia, on the other hand, they may occur in bone appearing otherwise perfectly normal by x ray. Indeed, the only x ray evidence of the bone disease may be these 'fracture' lines. These lines of 'fracture' in rickets and osteomalacia tend to be symmetrical and to occur over and over again at certain points,—the necks of the femurs the ramuses of the pubic and ischial bones, the ribs, *et cetera*. Perhaps the commonest of these sites is the axillary edge of the scapula (see Fig 105, p 209, and 128B, p 255). In conclusion, therefore, it may be stated that ribbon like zones of decalcification which occur in otherwise normal appearing bone which last months or years without regressing and which exhibit a marked tendency to be symmetrical, occur only in osteomalacia or rickets.

Albright, Burnett, Parson Reifenshtein and Roos (1946) reviewed the serum calcium, phosphorus, and phosphatase values in Milkman's classical case, in six new cases which they reported, and in nine cases from the literature, and found the values by and large to be consistent with osteomalacia.

The third piece of evidence that Milkman's syndrome is a form of osteomalacia has to do with the excellent responses one gets to therapy based on the assumption that the syndrome is a form of osteomalacia. Several of the cases reported in the literature have responded favorably to vitamin D therapy, others have not. As will be discussed below, there are several etiologies for osteomalacia and, unless one understands just what the etiology is one cannot obtain the best results. Those cases which are due to simple lack of vitamin D will respond to small doses of this agent, other cases will require other agents in addition. However, the evidence to be presented will make it quite clear that each etiological type of Milkman's syndrome responds to the correct therapy for overcoming osteomalacia of that particular type.

The difficulty in coming to a pathological diagnosis is twofold (A) most of the biopsies have been taken from the pseudofractures and (B) the osteomalacia in many cases is of a low degree. The histology of a callus is very complicated at best, and in a decalcified preparation it is most difficult to differentiate between a callus formed in normal bone and a callus formed in osteomalacic bone. Ham Tidall, and Drake (1938) found this out in experimental osteomalacia in rats (*vide supra*). Obviously, in a generalized bone disease such as osteomalacia, one should take one's biopsy away from the fracture site. Even this may not lead to a clear-cut diagnosis thus, in Case No 22 such a biopsy failed to show definite osteomalacia. This is perhaps understandable. In the normal adult skeleton bone formation is not very active since osteomalacia by definition is a generalized bone condition in which there is a failure of calcium salts to be

deposited in newly prepared osteoid, its diagnosis will be more difficult where very little osteoid is being laid down

Dr Granville A. Bennett of the Department of Pathology of the Harvard Medical School was able to make a definite diagnosis of osteomalacia on a pseudofracture from a rib of Case No. 21 (see Fig. 106 and 107), through the courtesy of Dr. Milkman, Dr. Bennett also had the opportunity to review the bone histology in his case and came to an almost definite diagnosis of osteomalacia

An inspection of Fig. 106 and 107 will leave no doubt as to the diagnosis of osteomalacia in this case. Furthermore, the bone tissue obtained at autopsy on Case No. 28 shows florid osteomalacia (see Fig. 129, p. 256). Thus, we have, as a fourth piece of evidence that Milkman's syndrome is a form of osteomalacia, the histological findings

Case No. 21 illustrates many of the points brought up thus far

Case No. 21. Milkman's syndrome, Osteomalacia of Undetermined Etiology

This case first brought Milkman's Syndrome to the attention of one of us (F. A.). The patient has never been seen by our Boston group but all the data have been supplied by a group of California investigators to whom the present authors are greatly indebted.*

The patient, Mrs. A. J., first consulted Dr. Smith in 1939 at the age of 37. Following the birth of her second child seven years previously she developed tiredness of the hips, pain in the back and difficulty in "picking up her heels". The condition progressed so that in 1939 she could walk only with crutches and had great difficulty getting up from a sitting position.

The points of interest in the past history were jaundice at 22 of short duration, absence of dental trouble, poor appetite, regular bowel movements, occasional digestive disturbances relieved by food or alkalis, and nocturia (three times).

Physical examination was non-contributory except for weight of 112½ pounds, deformities of the back and chest suggesting collapsed vertebrae, limitation of motion of the hip joints, white sclerae, and blood pressure of 120/80.

As regards the x-ray findings (see Fig. 108 and 109), the following quotations are taken from Dr. Stone's report of 9-21-36: "In almost all of the bones the number of trabeculae is decreased. In many places, particularly in the ribs, there are streaks of decreased density which closely resemble fractures. One would need to consider these all as fractures were it not for the fact that in some

* This group includes the late Dr. Arthur M. Smith of Oakland, California, who in 1940 first wrote one of us (F. A.) concerning the patient, Dr. Dudley W. Bennett of the University of California Hospital, San Francisco, who studied the patient extensively in 1937 and whose findings were transmitted to the authors, Dr. Robert S. Stone and Dr. Earl R. Miller of the University of California Hospital who made the x-rays of the patient available, Dr. Frederick C. Bost who took a biopsy of one of the ribs and Dr. Charles I. Connor of the University of California Hospital, San Francisco who sent the biopsy material for study by Dr. Granville A. Bennett.

places such as the scapulae and the pelvis, they do not completely cross the bone the periosteum overlying these areas of decreased density has been elevated, and in many places superiosteal new bone has been laid down the changes seen are almost bilaterally symmetrical thus we find that there is an area of this osteoid tissue resembling fracture on the axillary border of the right scapula about two inches below the glenoid whereas it is only about one inch below the glenoid on the left scapula (see Fig 105C and 105D) extending laterally from both sacroiliac joints into the respective ilea are short lines of the pseudofracture type on June 19, 1935 patient was examined for suspected fracture of the left hip and a line closely resembling a fracture line was seen in the middle of the

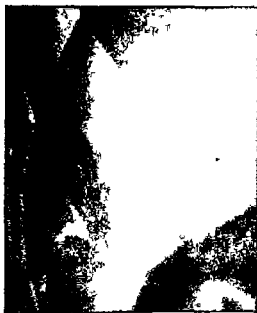


Fig 106 Case No 21, Milkman's Syndrome X ray Film Showing Pseudofracture of Rib

For microscopic appearance see Fig 107 [From Albright Burnett, Parson, Reifenstein, and Roos (1946)]

neck the necks of the femurs (later films) have become more slender and the heads have bent around this, in its completed stage as seen at the present date, resembles bilaterally slipped epiphyses "

The following laboratory studies taken while she was under the care of Dr Dudley W Bennett in 1936 are of interest serum calcium 10.7 mg per 100 cc, serum phosphorus 2.5 mg per 100 cc, serum protein 7.44 gm per 100 cc, blood creatinine 1.2 mg per 100 cc, urinary calcium excretion, while on a low calcium intake 0.007 gm per 24 hours (very low) serum phosphatase high on one determination and normal on the next

Subsequent studies on October 1937 showed serum calcium 10.2 and 10.6 mg per 100 cc, serum phosphorus 1.6 and 1.5 mg per 100 cc serum phosphatase 8.6 and 7.6 Bodansky units, and urinary calcium excretion 0.018 gm per 24 hours

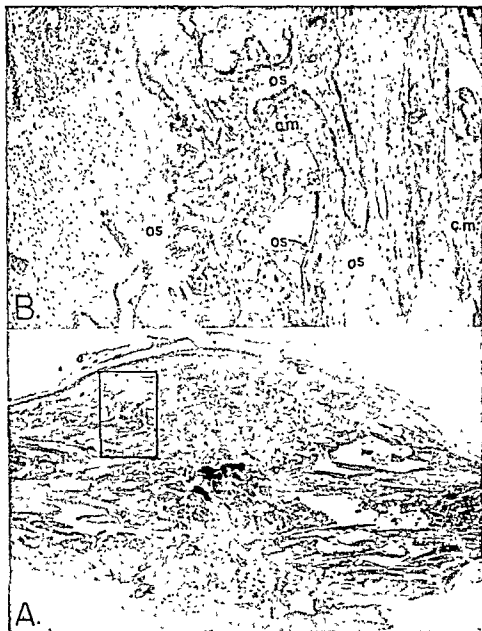


Fig. 107. Case No. 21; Milkman's Syndrome. Photomicrograph of Biopsy Through Pseudofracture of Rib.

(A) Low-power magnification of section through pseudofracture of rib (see Fig 106). (B) High power magnification of same. In "B" note large amount of osteoid (os) which contrasts itself very clearly from the calcified matrix (c.m.). The authors are indebted to Dr Granville A. Bennett for these histological sections. [From Albright, Burnett, Parson, Reifenstein, and Hoos (1916).]

In October 1941 the following serum determinations were made at the Samuel Merritt Hospital in Oakland, California: sodium chloride 600 mg per 100 cc content of CO_2 59.3 volumes per cent.



Fig 108 Case No 21 Milkman's Syndrome X-ray Films Showing Pseudofractures (Arrows) in Both Ulnae

Films taken 9-18-37 The authors are indebted to Dr Robert S Stone for these x-ray films [From Albright Burnett Parson Reifenstein and Poos (1946)]

A biopsy of one of the pseudofractures of the ribs was performed March 6 1940 by Dr Best The pathological diagnosis made by Dr Granville A Bennett was osteomalacia (see above)



Fig 109 Case 21, Milkman's Syndrome X ray Films of Pelvis Showing Pseudo fractures (Arrows)

Films taken on 6-10-35 (A), and 9-16-37 (B) In "A" note normal texture of bones except for "pseudofractures" X ray films furnished by Dr Robert S Stone [From Albright, Burnett, Parson, Reifenstein, and Roos (1916)]

The chemical findings—normal serum calcium, low serum phosphorus and high serum phosphatase—were consistent with osteomalacia. The x rays were those of Milkman's syndrome, a biopsy was diagnosed osteomalacia, there was little to suggest disorder of fat-soluble vitamins other than vitamin D, the serum chemistry was not that of renal acidosis, accordingly it was advised that the patient take large doses of vitamin D starting with 900 000 units daily. This therapy was started in February 1942. In one month she noticed marked improvement and by September 1943 was able to report that the pain was gone and that the bones and muscles were much stronger. She had taken vitamin D continuously but the exact amounts are not available.

(B) *Milkman's Syndrome is Ordinary Osteomalacia*

What is so peculiar to Milkman's syndrome that it should be separated from osteomalacia in general? The answer to this question, in the authors' opinion, is the co-existence of the pseudofractures and a skeleton which otherwise is not definitely abnormal as judged by x rays. When Dr Arthur M. Smith of Oakland, California sent the x rays and case history on Case No. 21 (*vide supra*) to one of us, he (F. A.) could not believe, in spite of the fact that the serum chemistry was that of osteomalacia, that this could be the diagnosis. It seemed unlikely that osteomalacia could have led to pseudofractures without having caused generalized demineralization (see Fig. 109A). The pseudofractures of course, are likewise seen in cases with extensive generalized demineralization. The authors now believe, therefore, that there is no sharp line of demarcation between Milkman's syndrome and classical osteomalacia, that the differences are quantitative rather than qualitative, but that the term Milkman's syndrome should be retained as an x ray diagnosis to call attention to the fact that one can have an underlying osteomalacia when the only x ray evidence is the ribbon like zones of decalcification.

IV. THE FOUR DEGREES OF OSTEOMALACIA

It is possible to separate cases of osteomalacia into four degrees with respect to their severity. (1) chemical-osteomalacia with normal phosphatase, (2) chemical-osteomalacia with high phosphatase, (3) Milkman's syndrome, and (4) advanced osteomalacia. The first degree of osteomalacia takes in those cases where there has arisen a disproportion of the serum calcium in relation to the serum phosphorus such that calcium is not deposited in newly formed osteoid, but where this disorder has not yet led to sufficient weakness of the skeleton as a whole to bring about an increased production of osteoblasts and hence a high serum phosphatase level. The second degree of osteomalacia takes in those cases where the condition has progressed to the point of stimulating osteoblastic activity but not to the extent of causing pseudofractures or obvious demineralization, and

where clinical or x ray evidence of bone disease is lacking. The third degree takes in those cases with chemical osteomalacia and pseudofractures but without obvious generalized demineralization. The fourth degree is reserved for those cases with out and out bone disease.

V. ETIOLOGIES OF OSTEOMALACIA MET IN THE UNITED STATES

(A) Classification

A classification of the etiologies of the various forms of osteomalacia met in the United States is given in Table 5.

(B) Osteomalacia Resulting from "Simple" Vitamin D Lack

By the expression, "osteomalacia resulting from simple vitamin D lack", the authors have in mind a condition like the usual variety of infantile

TABLE 5

Etiologies of Osteomalacia Met in the United States

-
- | |
|--|
| A) Vitamin D Lack |
| a) Simple" Vitamin D lack |
| b) Resistance to Vitamin D |
| c) Steatorrhea |
| B) Renal Acidosis |
| a) Tubular Insufficiency Without Glomerular Insufficiency |
| b) Fanconi Syndrome |
| C) Idiopathic Hypercalcaemia |
| D) Hyperparathyroidism with Osteitis Fibrosa Generalisata during Transitional State following Removal of Parathyroid Tumor |
-

rickets where the bone disease is responsive to small doses of vitamin D. It is appreciated, of course, that in a case of osteomalacia which is curable by small amounts of vitamin D there may be other contributing factors such as lack of exposure to sunlight, lack of calcium and phosphorus in the diet, *et cetera*. Indeed, the patient with infantile rickets who is healed by small doses of vitamin D has, as a contributing factor, growth with its new bone formation.

The authors are cognizant of no single case of osteomalacia in the United States due to simple vitamin D lack as defined above. And yet Maxwell (1935) states that in Northern China there are 100,000 cases of osteomalacia and osteomalacia in China responds to small doses of vitamin D. The condition in that country is, according to Maxwell (1935), the result of a combination of circumstances. The food is practically devoid of animal fat and hence of vitamin D, in addition, the diet is low in calories, protein,

calcium, and phosphorus, finally, many of the women in this northern climate never go out of doors and so get very little exposure to sunlight.

Hannon, Liu, Chu, Wang, Chen, and Chou (1934) and Liu, Hannon, Chu, Chen, Chou, and Wang (1935) have carried out interesting metabolic studies on Chinese patients. These show in the control periods before the administration of vitamin D large fecal excretions of calcium and phosphorus and—most important!—an almost complete lack of calcium in the urine, with vitamin D administration fecal excretions are decreased and the balances much improved. One of their studies is re-charted in Fig. 110.

The nearest approach, in adult medicine in this country, to these cases of osteomalacia in China to come to the attention of the authors is a case report in 1930 by Gargill, Gilligan, and Blumgart (1930). This concerned a 38 year-old woman with advanced osteomalacia (normal serum calcium, low serum phosphorus, high serum phosphatase) who responded to small doses of vitamin D. The original metabolic studies are re-charted in Fig. 63, p. 129 and some new studies carried out in this clinic on the same individual in 1945 are charted in Fig. 111. The striking fact brought out by both of these studies is the high urinary calcium excretion (*circa* 200 mg daily in the more recent studies) which remains relatively constant regardless of the regimen, the fecal calcium and phosphorus excretions are not unduly high, the calcium balances become strongly positive with small doses of vitamin D or even without vitamin D (see Fig. 111, periods 1 to 3) provided the calcium intake is sufficiently large so that the absorbed calcium is greater than the calcium lost in the urine. The present authors conclude that the etiology of the osteomalacia of this patient is fundamentally dissimilar to that of the Chinese patients and is not primarily due to simple lack of vitamin D, the authors ascribe the initial defect to a propensity on the part of the kidneys to excrete calcium in increased amounts at a normal level of serum calcium. This category of osteomalacia will be discussed briefly below (p. 260). That the Chinese variety of osteomalacia occurs in the United States, to the authors' knowledge, remains undemonstrated.

(C) *Osteomalacia Resulting from Resistance to Vitamin D*

In 1937 Albright, Butler, and Bloomberg (1937) published a case (W. M., M. G. H. 325488 and M. G. H. 91422) of late rickets in which they ascribed the defect in metabolism to a resistance to the action of vitamin D. In spite of what would be usually considered as adequate vitamin D therapy, this patient had had rickets all his life, the abnormalities in his calcium and phosphorus metabolism were the same as those in ordinary infantile rickets,

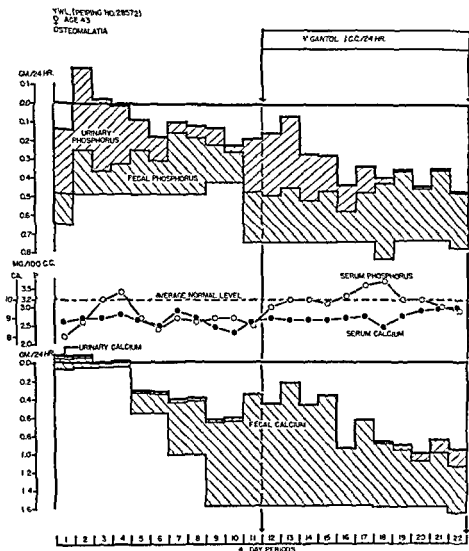


Fig 110 Metabolic Study on Patient with Osteomalacia as It Occurs in China
For explanation of construction of chart see Appendix, page 309

Fig 110 is self-explanatory. Note especially extremely low urinary calcium excretion until period 19 marked fall in urinary phosphorus excretion with rising serum phosphorus during periods 11 through 18 rise in urinary calcium excretion when urinary phosphorus excretion becomes negligible which indicates that calcium cannot be retained without phosphorus (see periods 19 through 22), and the strongly positive calcium and phosphorus balances even before administration of the vitamin D preparation, Vigantol. These pre medication positive balances are probably to be attributed not only to the high calcium intake, but to the vitamin D content of the experimental diet [From Albright, Burnett, Parson Reiserstein and Roos (1946), recharted from Liu, Hannon, Chu, Chen, Chou, and Wang (1935), with permission of Dr R. R. Hannon and the Chinese Medical Journal]

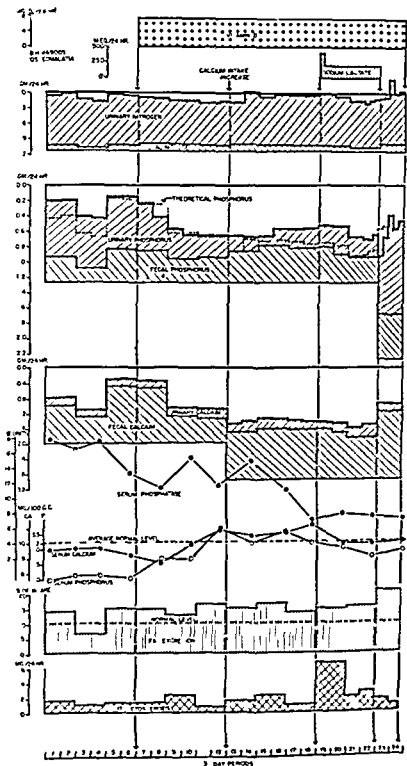


FIG III

namely normal calcium, low phosphorus, and high phosphatase levels in the serum, and an increased partition of calcium and phosphorus in the feces, the usual dosage of vitamin D had no effect on these abnormalities, however, massive doses of vitamin D (450 000 I U daily) did correct them.

Two metabolic studies on this patient five years apart are re-charted in Fig 112. In the first of these studies it will be noted that the fecal calcium excretion was not appreciably lowered by 150,000 units of vitamin D for nine days and by 300,000 units of vitamin D for an additional three days. A third metabolic study on this same patient is shown in Fig 60 (p 124) where it will be seen that 600 000 units of vitamin D daily caused a definite decrease in fecal calcium in six days. For contrast note the rapid decrease in fecal calcium excretion in a study on a patient with osteomalacia associated with steatorrhea during the first three days of a relatively small dose of vitamin D (see Fig 59, p 123). In the second study in Fig 112 on the patient with vitamin D resistant rickets it should be noted in passing that the fecal calcium excretion decreased markedly in the first three days of treatment with 12 5 mg daily of dihydrotachysterol (10 cc of A T 10), this, of course, was a massive dose so one cannot conclude that this patient is non resistant to dihydrotachysterol.

It was the belief of Albright, Butler, and Bloomberg (1937) that, wherever vitamin D has its primary action in that place in this patient there existed a resistance to the action of vitamin D, it was not their conception that this patient suffered from some endogenous error in calcium or phosphorus metabolism, such as idiopathic hypercalcaemia (see p 260) which would necessitate increased calcium absorption and hence more vitamin D to prevent a negative calcium balance.

Fig 111 Metabolic Study on Patient with Osteomalacia Resulting from Idiopathic Hypercalcaemia

For explanation of construction of chart see Appendix, page 303

Subject of this experiment carried out in 1945 at the Massachusetts General Hospital was the same patient studied by Gargill, Gulligan and Blumgart (1930) (see Fig 63, page 129). The figure is self explanatory. Note especially the strongly positive calcium balance during the pre medication periods (1 through 6) which suggests that the hospital diet contained more calcium or more vitamin D or more of both than the diet which the patient received at home, note the relatively high and rather constant urinary calcium excretion in this patient with marked osteomalacia note as in Fig 110 the rising serum phosphorus level with the falling urinary phosphorus excretion on administration of vitamin D which combination of findings suggest decreased parathyroid activity and note the falling serum phosphatase level after a continued positive calcium balance. Attention is called to the lack of effect of sodium lactate administration (period 19 through 22) on the calcium balance which is strong evidence that the hypercalcaemia is not due to some form of acrolosis. [From Albright, Burnett, Parson, Reifenstein and Roos (1946)]

This patient has been carefully followed to see what would happen to the disordered calcium and phosphorus metabolism when the patient ceased

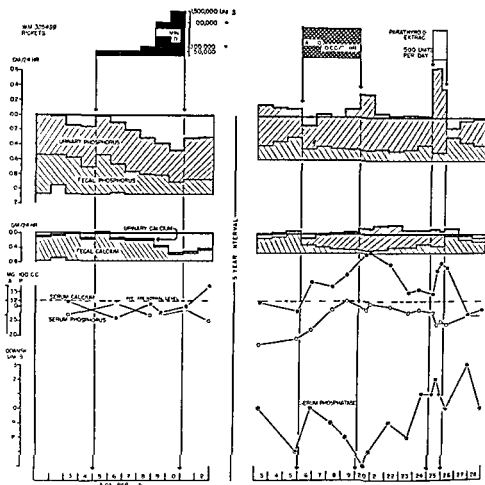


Fig 112 Metabolic Data on a Patient (W M, MGH 325488) with Vitamin D Resistant Rickets

For explanation of construction of chart see Appendix, page 309

This chart is introduced to bring out the difference in the actions of vitamin D dihydrotachysterol and parathyroid hormone. Some caution has to be exercised in comparing the effects of vitamin D with the other two since this part of the experiment was carried on five years before the other part. For further discussion, see text. [From Albright, Burnett, Parson, Reifenstein, and Roos (1946), recharted from Albright, Sulkowitch, and Bloomberg (1939)]

growing. In Fig 113 are charted the serum calcium, phosphorus, and phosphatase values in relation to his age, height, and vitamin D therapy. This chart is a continuation of that shown as Fig 8 in the paper by Al-

bright, Butler, and Bloomberg (1937). It will be seen that growth ceased about January 1939 at the age of $18\frac{1}{2}$ years and that vitamin D was omitted in February 1940. It will be further noted that, although the patient has remained symptom free and able to work at a war job, the serum phosphorus level has continued low and the serum alkaline phosphatase

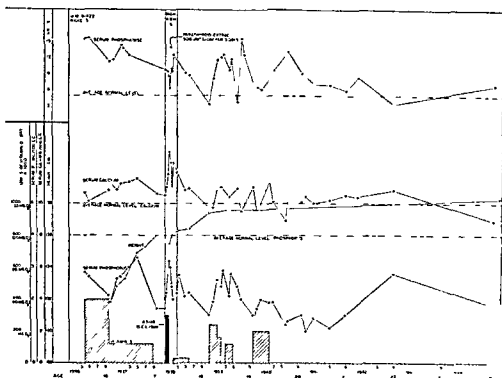


Fig 113 Effect of Maturation of Skeleton (Cessation of Growth) on Serum Calcium, Phosphorus, and Phosphatase Levels in a Patient with Vitamin D Resistant Rickets.

For further discussion see text [From Albright, Burnett, Parson, Reifenstein, and Roos (1916)]

level high during the five years since the omitting of vitamin D. His epiphyses being now united, his diagnosis becomes "chemical osteomalacia with-high-phosphatase".

(D) Hypovitaminosis D Secondary to Steatorrhea

Perhaps the commonest form of hypovitaminosis D in adults is where the primary difficulty is a steatorrhea. Vitamin D, being fat-soluble, is not absorbed; the same holds for other fat-soluble vitamins. Therefore, such patients differ from the others in that they have, in addition to

hypovitaminosis D, deficiencies in the other fat soluble vitamins notably A and perhaps E [Albright and Stewart (1940)]

The two chief causes of steatorrhea in this country are (1) an idiopathic steatorrhea which masquerades under the diagnosis of non tropical sprue or in children under the diagnosis of coeliac disease or Gee's disease and (2) chronic pancreatitis. The latter differs from the former in several respects: the duodenal contents are markedly deficient in pancreatic ferments; a larger percentage of the fat in the stools is in the form of neutral fats as opposed to fatty acids and soaps; meat fibers are often present in the stools and the fecal nitrogen excretions are increased; the glucose tolerance is normal rather than increased, normal gastric acidity rather than hyp acidity is the rule. A third cause of steatorrhea is insufficiency of the small intestine resulting from any one of a number of causes: often some sort of circuiting operation, in the case reported by Albright and Stewart (1940) the small intestinal insufficiency was the result of terminal ileitis plus several operative procedures.

The diagnosis of osteomalacia secondary to steatorrhea often remains unrecognized for a long period of time, especially in those cases where diarrhea is not a prominent feature. Thus Case No. 22 underwent a gall bladder exploration because it was not recognized that the pain in her right upper quadrant was due to a fractured rib. She then masqueraded under the diagnosis of Marie Strumpel arthritis because some thoracoplasty introduced into the sub arachnoid space in an attempt to find a ruptured disc as the cause of her symptoms was deposited on the dura (see Fig. 114) and was mistaken for calcified ligaments. Finally X rays taken to evaluate the degree of arthritis showed the characteristic findings of Milkman's Syndrome and the correct diagnosis was arrived at. As so often is the case once suspected the diagnosis offers no difficulties. The serum carotinoid and vitamin A contents should be decreased and the prothrombin time increased. A fecal fat value over 10 per cent of the intake or over 25 per cent of the dried fecal weight is strongly suggestive of steatorrhea. The characteristic blood chemistry findings of osteomalacia (*vide supra*) should be present. A number of the cases [e.g. case reported by Bauer, Marble, and Clafin (1932)] have had instead of a low serum phosphorus and a relatively normal serum calcium level a normal serum phosphorus level and a low serum calcium level with tetany. Presumably in such cases there has been *no compensatory hyperplasia of the parathyroids* (*vide supra*).

The treatment consists in correction of the steatorrhea if possible as by the administration of crude liver extract or folic acid in the case of non tropical sprue. If this is not possible a low fat diet should be prescribed and the fat soluble vitamins should be given in large amounts between meals so that they escape being dissolved in what little fat is present. The

most important thing is not to forget to give all the fat soluble vitamins rather than just the one, the lack of which is causing the most impressive symptoms. Thus, in Case No 22 it was not until large amounts of vitamin E in the form of alpha tocopherol were given that the patient's strength returned. The serum carotinoid level in a patient treated with all the fat soluble vitamins serves as an index to whether or not there is an improvement in the underlying process, thus, the blood vitamin A level will rise with vitamin A therapy while the carotinoid level will only rise if there is an improvement in the underlying gastro intestinal pathology.

Case No 22 Steatorrhea (Non Tropical Sprue), Hypovitaminosis D, K, A, and E, Osteomalacia (Milkman's Syndrome), Thoratrast Impregnation of Dura

E M (M G H 395551), a housewife of 30, first entered the Massachusetts General Hospital as a patient of Dr William A Rogers on March 5, 1943 because of generalized skeletal pain. Her first symptoms started 12 years previously shortly after her first and only pregnancy, when she noticed pain in her feet while walking on rocks while stream fishing. Later she noticed easy fatigability and for about two years girdle pains in her mid trunk region. Although she tended to be constipated, she did admit of episodes of diarrhea at which time her stools were very bulky. She lost from her best weight of over 100 pounds down to 73 pounds.

Because of the pain in the right hypochondrium she underwent a gallbladder operation but no abnormality was found.

Her past history was irrelevant except for an appendectomy 10 years previously and a thyroidectomy for nontoxic adenoma 7 years previously.

On February 11, 1942 she received thoratrast intraspinally in an effort to demonstrate a ruptured disc, none was demonstrated.

On physical examination she was exceedingly weak, she was unable to raise her head off the pillow. Her ribs were very tender, her abdomen was distended and showed very little peristalsis. There was a muddy brown pigmentation of her face such as is seen in pregnancy. The pigmentation also involved the creases of her hands and the gallbladder scar but not the appendix scar.

Laboratory studies: urine normal, hemoglobin 14.0 gm/100 cc, white count 4,800, sedimentation rate normal, Hinton test for syphilis negative, phenolsulphonphthalein excretion excellent, stools negative except for moderate amounts of fat, mostly in the form of fatty acids. The chemical analysis showed serum protein 7.3 gm per 100 cc, serum calcium 8.7 mg per 100 cc, serum phosphorus 1.0 mg per 100 cc, serum alkaline phosphatase 10.8 Bodansky units, serum non protein nitrogen 18.0 mg per 100 cc, serum total cholesterol 108 mg per 100 cc, serum chloride 103.0 m eq per liter, serum CO₂ content 19 m eq per liter (21.0 m eq per liter in a repeat determination), and serum sodium 144.0 m eq per liter. The 17 ketosteroid excretion and the rate of growth of axillary hair were within normal limits. As evidence of vitamin K deficiency she had a prolonged prothrombin time 33 seconds as compared with the normal of 22 seconds as evidence of vitamin A deficiency, she had a decreased amount of vitamin A in

her blood, 0.4 units per cc (normal equals 1.5 units per cc), and no carotinoids. Her gastric acidity was normal, the creatinine excretion was very low (457 mg per 24 hours), while the creatine excretion was high (662 mg per 24 hours). Liver function tests were normal. Pancreatic ferments were found to be normal in the duodenal contents by Dr. Martin M. Nothmann of the Pratt Diagnostic Hospital, to whom the authors are very much indebted.



Fig 114 Case No 22, Steatorrhea, Milkman's Syndrome. X-Ray Films to Show Impregnation of Dura with Thoratrast

(A) Lateral view of thoracic vertebrae, (B) anterior posterior view of cervical and upper thoracic vertebrae. Note in "B" impregnation of dural sheaths of spinal nerves as they leave spinal column (see arrows). [From Albright, Burnett, Parson, Reifenstein and Hoos (1916)]

X rays showed impregnation of the entire dura of the cord and brain with thoratrast (see Fig 114). Generalized decalcification was thought to be present, and the lamina dura about the teeth was absent. The left second and third metatarsal bones showed united uncalcified fractures, there were multiple similar fractures of the ribs, one in the ascending ramus of the right pubic bone, one in the descending ramus of the left ischium, and finally one in the left scapula (see Fig 105f). The x rays also demonstrated marked hypoperistalsis of the small bowel with puddling.

The diagnoses made were non tropical sprue, hypovitaminosis with respect to all the fat-soluble vitamins, and osteomalacia with Milkman's Syndrome. Accordingly she was treated with large amounts of the four fat-soluble vitamins, a low fat diet, desoxycholic acid and liver extract (at first a pure preparation but later, on advice from Dr. Edwin J. Kepler of the Mayo Clinic a crude preparation). On this therapy her united but uncalcified fractures promptly calcified, her vitamin A level and prothrombin time returned to normal, but she continued to be very weak. Testosterone propionate was administered, 25 mg three times a week, with some improvement in strength and reduction of creatine excretion to zero. After 7 weeks of therapy and 4 weeks of testosterone injections, her vitamin T dosage was changed from 2 cc of wheat germ oil daily by mouth to 25 mg of alpha tocopherol three times daily. This change was attended by a most dramatic increase in body strength. She continued to be distended, however. For this she was given acetyl beta methyl choline chloride (Mecbolyl), 10 mg intramuscularly three times a day with marked relief. On discharge from the hospital two and one half months after onset of therapy her serum calcium was 9.9 mg per 100 cc, her serum phosphorus had returned to normal 3.3 mg per 100 cc, and her serum phosphatase was still above normal 14.0 Bodansky units.

The patient was last seen in July 1944. She had done quite well on the whole. However, x rays still showed poor peristalsis and the carotinol content of the blood remained negligible, indications that the underlying pathology was still present. A later gastric analysis had shown no free hydrochloric acid even after histamine. She had now no skeletal symptoms but continued to show a chemical osteomalacia, her last blood values being serum calcium 9.2 mg per 100 cc, serum phosphorus 3.6 mg per 100 cc, and serum alkaline phosphatase 10.4 Bodansky units.

(E) *Renal Acidosis Resulting from Tubular Insufficiency Without Glomerular Insufficiency**

Two important functions of the kidney tubules, to make ammonia and to excrete an acid urine, have to do with the conservation of base. Therefore, in the presence of damaged kidney tubules one might expect a scarcity of base with which to excrete acid. In this eventuality calcium, being a base, will be in demand and will appear in increased amounts in the urine. The serum calcium level will tend to fall. The sequence of events from here on will be the same as in vitamin D deficiency: the tendency to a low serum calcium level will lead to parathyroid hyperplasia, this will counteract the tendency to a low serum calcium level and will lead to hypophosphatemia, in the presence of a normal or slightly low serum calcium level and a low serum phosphorus level, calcium will not be deposited in osteoid and osteomalacia will result, the uncalcified new bone tissue will be less resistant to stresses and strains, this will lead to increased stimulation.

* By "insufficiency" the authors mean impairment of such a degree that the function in question is not carried out. The combination of an impaired urea clearance and a normal serum N P N level would be considered as evidence of glomerular impairment, but not of glomerular insufficiency.

of the osteoblasts and to a high serum phosphatase level. It will be seen later that if there is a glomerular insufficiency along with the tubular insufficiency the above sequence of events is interrupted at one stage.

The disruption of homeostasis with renal acidosis resulting from tubular insufficiency is not confined to the above sequence. Potassium, being a base, also tends to be excreted in excess in the urine. The hyperkalemia may lead to hypokalemia and to the low potassium syndrome similar to that seen in family periodic paralysis. This aspect of renal acidosis has already been discussed in a paper from this hospital by Brown, Currens, and Marchand (1944). Case No. 27 (see p. 203) who was first reported in this previous communication had episodes characterized by pain in the extremities and inability to move arms and legs; these episodes were accompanied by a low serum potassium level and the characteristic changes in electrocardiogram (notably a lowering of the T waves) which one finds with hypokalemia. Case No. 28 (see p. 204) almost certainly developed the low potassium syndrome as a complication of a severe acidosis just before she died; unfortunately no chemical or electrocardiographic evidence of hypokalemia was sought. Finally Case No. 23 (see p. 237) in an experimental study wherein she received for five days 130 mEq of ammonium chloride daily, developed the prodromal symptoms of low serum potassium while the serum potassium fell and the potassium excretion in the urine mounted (see Fig. 126, p. 248).

Another possible ramification of the disordered electrolyte metabolism in tubular acidosis has to do with calcium absorption from the gastrointestinal tract. Browne and Vineberg (1932) have shown that gastric acidity is decreased in acidosis. This would tend to decrease the calcium absorption from the gastro-intestinal tract and would be another factor favoring the production of osteomalacia.

The present authors, contrary to the previously expressed opinion of Albright, Consolazio, Coombs, Sulkowitch, and Talbott (1940), now believe that the nephrocalcinosis and the nephrolithiasis which frequently accompany this form of renal acidosis are complications of the disturbed homeostasis rather than causes. One strong piece of evidence in favor of this point of view lies in the fact that one meets essentially the same disturbance of homeostasis in cases without nephrocalcinosis or nephrolithiasis as in cases with these complications. Thus the present analysis is based on eight cases; two of these (Case No. 23 and Case No. 24) had neither nephrolithiasis nor nephrocalcinosis; two cases (Case No. 27 and Case No. 28) had nephrolithiasis without nephrocalcinosis; four cases [case reported by Butler, Wilson, and Farber (1936), case reported by Albright, Consolazio, Coombs, Sulkowitch, and Talbott (1940), Case No. 20, and Case No. 26] had both nephrolithiasis and nephrocalcinosis (see Fig. 110). A second

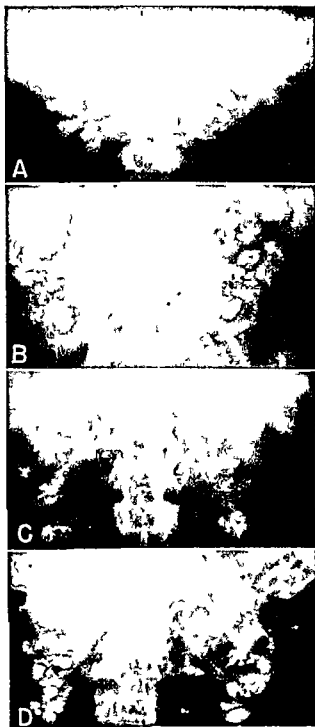


Fig. 115 X Ray Films on Four Cases with Renal Acidosis and Nephrocalcinosis to Show Similarity

(A) Case of Butler, Wilson and Farber (1936), (B) case of Albright, Conzelmann, Coombs, Sulkowitch, and Talbott (1910), (C) Case No. 25, (D) Case No. 26 [From Albright, Burnett, Parson, Reifenstein and Roos (1916)]

argument in favor of the nephrolithiasis and nephrocalcinosis being secondary phenomena lies in the fact that these cases when treated with alkali, do not form more stones, indeed, since they continue to pass some

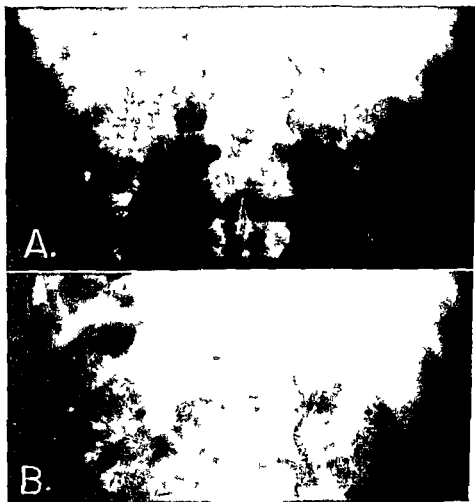


Fig 116 Case No 25 Renal Acidosis and Nephrocalcinosis X ray Films of Kidneys to Show Marked Diminution in Number of Stones

(A) X ray on 7-16-41 (B) x ray on 10-13-44 [From Albright Burnett Parson Reifenstein and Roos (1946)]

of the stones the number left in the kidneys often decreases. Since alkali therapy lowers the calcium excretion in the urine this suggests that the hypercalcaemia is the cause of the stones. The case reported by Albright Consolazio Coombs Sulkowitch and Talbott (1940), Case No

25, and Case No 26 all showed with alkali therapy a decrease in the number of stones (see Fig 116) Case 3 reported by Albright, Burnett, Parson, Reifstein, and Roos (1946) and Case No 23 without kidney calcification did differ from the group as a whole in one respect—the ability to concentrate the urine Thus, the specific gravity of the urine reached 1 028 in case 3 and 1 018 in Case No 23, Case No 27 with nephrolithiasis but not nephrocalcinosis likewise had a urine specific gravity of 1 018 but the gravities of none of the other cases exceeded 1 012 This ability to concentrate the urine despite marked tubular insufficiency, in case 3 and Case No 23, is a very interesting fact and may be an important clue It suggests that the original tubular pathology does not involve the loops of Henle where most of the water is reabsorbed This lack of hyposthenuria by allowing urinary concentration, would favor precipitation of calcium in the tubules and the authors believe that the hyposthenuria present in those cases with nephrocalcinosis is at least one feature which is the result of the nephrocalcinosis

In Fig 117 are depicted in diagrammatic form the relationships, one to the other, of the metabolic abnormalities in the syndrome under discussion

It should be pointed out at this point that the condition under discussion and so called "renal rickets" are two entirely different entities The latter condition as pointed out by Albright, Drake, and Sulkowitch (1937) is not rickets at all but osteitis fibrosa generalisata (see p 115) As regards the bone pathology in renal rickets, the emphasis is on increased bone destruction as opposed to lack of calcification of newly formed osteoid To be sure, Ellis and Jackson (1943) have shown that even in renal rickets there is some delay in the calcification of newly formed osteoid the present authors agree with this point of view As a matter of fact, the published photomicrographs of the case reported by Albright, Drake and Sulkowitch (1937) are found on re-examination to show the osteoid seems to be slightly wider than normal (see Fig 58, p 120) A fundamental difference in these two osteonephropathies lies in the kidney pathology itself in the condition under discussion, one finds tubular dysfunction with relatively little glomerular insufficiency The tubular insufficiency in renal rickets makes the first step in the derangement of homeostasis the same as in the condition under discussion, namely there is a decreased ability to make ammonia and to excrete an acid urine, this leads to a demand for calcium for excretion in the urine as a base this to a tendency to a low serum calcium level, this in turn to parathyroid hyperplasia, but here the sequence is interrupted! Because of the glomerular disease, the increased parathyroid hormone does not produce a phosphorus diuresis and lower the elevated serum phosphorus level resulting from phosphorus retention, with a high serum phosphorus level there cannot be much delay in the deposition of

calcium into the newly formed osteoid. Furthermore in renal rickets there is usually marked retention of urea, creatinine, uric acid, sulphate, and potassium, and considerable impairment of phenol ulphonphthalein excretion. The acidosis in renal rickets, in short, is due not only to a shortage of base but to a retention of acid radicals; therefore it is not immediately corrected by the giving of base. In Fig 118 are depicted in diagrammatic form the relationships, one to the other, of the metabolic abnormalities of renal osteitis fibrosa generalisata. This figure is to be contrasted with Fig 117.

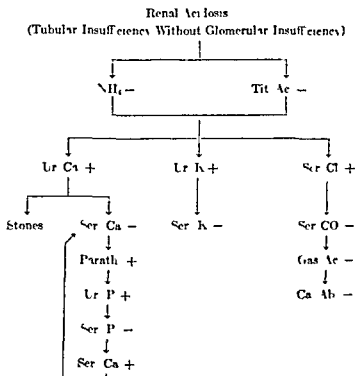


Fig 117 Sequence of Events in Disorderd Homeostasis Resulting from Periodic Acidosis of the Tubular Insufficiency Without Glomerular Insufficiency Type [From Albright, Burnett, Parson, Reifenstein, and Poon (1946)]

The etiology of the original kidney pathology in renal acidosis resulting from tubular insufficiency without glomerular insufficiency remains obscure. One first thinks of an ascending infection of the tubules from a pyelonephritis. The actual evidence for this in eight well advanced cases, however, is slight. Only in Case No 25 and possibly in Case No 27 were urinary infections demonstrated. The case reported by Albright, Connolly, Coombs, Sulkowitch, and Talbott (1940), Case No 23, Case No 24, Case No 26, and Case No 28 all had negative urinary cultures. There

were no urinary cultures reported in the case of Butler, Wilson, and Farber (1936). The autopsy findings in the kidneys in Case No. 28 (see p. 256) are interesting but not too clear-cut. The fact that most of the glomeruli were uninvolved fits the clinical picture. It is also consistent that the most important changes were in the convoluted tubules. On the other hand, there was evidence of a low grade or a healed pyelonephritis. Boyd and Stearns (1941) reported a similar case which showed only slight calcium deposits in the pyramids while the tubules were essentially normal though the convoluted tubules were considerably dilated. Barnes, Barclay, and Cooke (1945) reported a very interesting case. The patient, a 29 year old woman, had bilateral renal stones, an elevated serum chloride level, a decreased plasma bicarbonate level, and a relatively fixed urinary

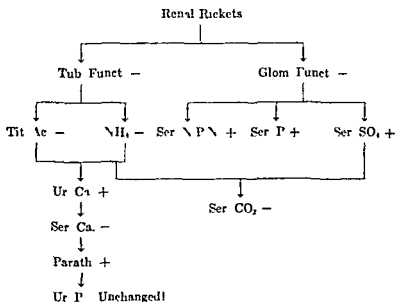


Fig. 118 Sequence of Events in D bordered Homeostasis with Renal Rickets. Compare with Fig. 117 [From Albright, Burnett, Parson, Reifenstein, and Roos (1946)]

specific gravity and pH, she responded to sodium citrate-citric acid therapy, she died after a severe reaction to sulfathiazole. Preliminary histopathological examination of the kidneys showed calcification in the pyramids and renal pelvis but negligible amounts within the tubules and kidney tissues. The tubules themselves showed extensive vacuolation and an alteration in the type of epithelium. Occasional glomeruli were atrophied. There was no evidence of primary chronic vascular disease or glomerulonephritis. The authors felt that the findings were consistent with a non-inflammatory tubular defect. Thus the nature of the primary pathological lesions

remains obscure—whether metabolic or enzymatic whether infectious whether degenerative

The authors believe that renal acidosis of the sort under discussion leading to nephrocalcinosis and nephrolithiasis and at times to osteomalacia is relatively rare. It is probably idiopathic hypercalcaemia (discussed on p 260) and not the type of renal acidosis now being discussed which largely accounts for the findings of Flocks (1940) this investigator noted that a large number of patients with renal calculi have hypercalcaemia coupled with a disproportionate increase in urinary calcium excretion when vitamin D or an acid ash diet are given

The response to treatment in these cases is most spectacular (see Fig 119 120 and 121) and since the treatment is based on the theoretical considerations just discussed the validity of the theories is strengthened thereby. Inasmuch as the initial disturbance is a shortage of base the first item of treatment is the administration of base. This is best given in the form of a salt of a mineral base with an organic acid e.g. sodium citrate sodium lactate or calcium gluconate or if hypokalaemia is a factor a combination of sodium citrate and potassium citrate. The organic acid is burned after absorption leaving the base free to help in the excretion of acid in the urine. An organic acid such as citric acid which will be largely burned after absorption can be given in addition to increase the gastrointestinal acidity and hence favor calcium absorption. The prescription advocated by Dr Alfred T Shohl and used by Albright Consolazio Coombs Sulkowitch and Talbott (1940) consisted of 140 grams of citric acid and 98 grams of sodium citrate dissolved in one liter of water the patient takes 50 to 100 cc of this mixture daily depending on the amount needed to overcome the acidosis. Whereas such alkali therapy by itself will quickly restore the serum chloride level and CO_2 content to normal it will not cure the osteomalacia—at least not in a short period of time. Since the cause of the osteomalacia in the first place is a shortage of base the above statement at first seems contradictory. The explanation is probably one of simple arithmetic. The normal adult absorbs relatively little calcium (in round numbers let us say 100 mg daily) and if in calcium equilibrium excretes in the urine an amount equal to that which is absorbed*. If this individual now develops renal acidosis of the type under discussion the calcium excretion in the urine may reach 300 to 500 mg daily this will mean a loss to the body of 200 to 400 mg daily if this goes on for months and years the skeleton will become depleted and the elevated calcium excretion in the urine will somewhat decrease. Now if one overcomes the acidosis with alkali therapy one can prevent further loss but the

* In this arithmetic the amount of calcium absorbed and re excreted in the bile is disregarded

most one can hope to achieve in the way of a positive balance is 100 mg per day if the calcium excretion in the urine should fall to zero, but since the parathyroid hyperplasia keeps the serum calcium up to normal there will be some loss of calcium in the urine and the positive balance will be less than 100 mg per day. Therefore, the second step in therapy is the administration of an agent which will increase the calcium absorption from

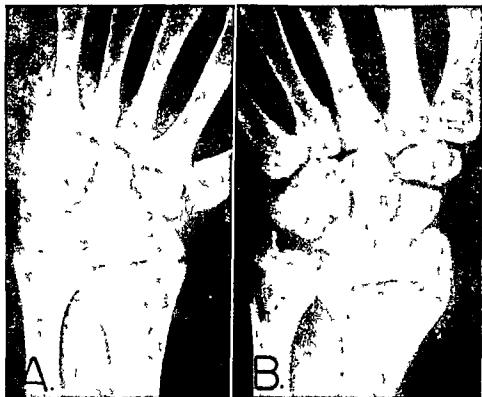


Fig. 119 X-Ray Films of Wrist on Case No. 21 with Rickets Resulting from Renal Acallosis (A) Before (1-10-33) and (B) After (2-21-33) Healing of Rickets with Massive Doses of Vitamin D

[From Albright, Burnett, Parson, Reifenstein and Roos (1916)]

the gastro-intestinal tract, namely vitamin D. A combination of this with alkali therapy will bring about the desired end. Thus, vitamin D will cause calcium to be absorbed, alkali therapy will decrease its loss in the urine. If vitamin D is given alone a large part of the calcium which is absorbed will be re-excreted in the urine. If alkali therapy is given alone, very little calcium will be absorbed so that in spite of little loss in the urine the balance will still be only slightly positive. As a matter of fact if one gives a very high calcium intake and massive doses of vitamin D, so much

calcium will be absorbed that in spite of the large loss in the urine the patient will be in positive calcium balance and the osteomalacia will be cured (see Fig 119). Once the osteomalacia is cured alkali therapy alone will prevent further bone disease and continuation of vitamin D in massive

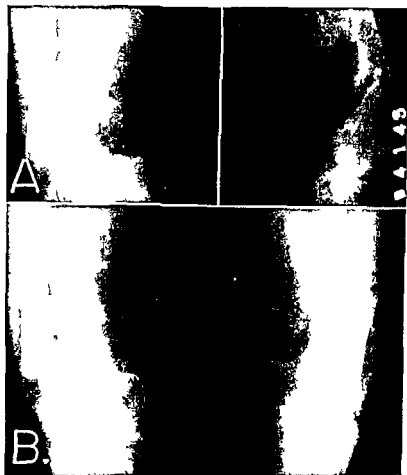


Fig 120 Case No 96 Real A dose with Osteomalacia and Nephrocalcinosis
X-ray Films of Femurs to Show Effect of Therapy

(A) X-ray on 4-1-43 and (B) X-ray on 7-4-43. Note that calluses of lateral osteotomy performed on 6-25-42 were only incompletely calcified on 4-1-43 before therapy. [From Albright, Burnett, Parson, Reifenstein, and Roos (1946)]

doses is not only not necessary but may lead to hypervitaminosis (see p 95).

The above treatment not only results in the alleviation of the bone disease but restores normal growth where the epiphyses are not yet united.

The lack of skeletal growth in rickets has been attributed by some to a disorder other than that in the calcium metabolism. It is possible however to draw up a reasonable hypothesis to explain it on the basis of the disordered calcium metabolism. Thus the sequence of events might be (1) relative unsaturation of body fluids with calcium phosphate (2) failure of calcification of the zone of provisional calcification of cartilage (3)



Fig. 121. Case No. 26. Renal Acidosis with Osteomalacia and Nephrocalcinosis. X-ray films of Abdomen and Pelvis to Show Effect of Therapy.

(A) X-ray film on 3-30-43. (B) X-ray film on 12-21-44. In A note increased radiolucency of bones, fractures on pubic ramus, stones in lower end of right ureter, marked scoliosis and bilateral nephrocalcinosis. In B note normal density of bones, decreased degree of scoliosis, new collection of stones at lower end of right ureter and decrease in number of kidney stones. [From Allright, Burnett, Parson, Reifenstein and Roos (1946)].

failure of mature cartilage cells to die (4) failure of blood vessels to break into holes left by dead cartilage cells (5) continuation of proliferation of cartilage cells (6) an increasing distance between proliferating cartilage cells and blood supply and (7) failure of cartilage cells to proliferate due to lack of blood supply.

Case No. 23. Renal Acidosis. Milkman's Syndrome

M. S. P. (MCH 237547) a 40-year-old white married laundress first entered the Outpatient Department in February 1940 complaining of back pain for sev-

eral years and of pain and stiffness of the fingers of the left hand for one and one half years. She had lost 20 pounds in the preceding two years.

Physical examination revealed moderate atrophy of the left forearm, and severe atrophy of the left third, fourth, and fifth fingers. There was marked hyperesthesia of these parts.

Initial x-ray examination showed severe decalcification of the left hand, most marked in the third, fourth and fifth fingers. There was a pseudofracture of the left scapula (see Fig. 105F), the significance of which was not appreciated at that time. The spine was decalcified and showed scoliosis and kyphosis.

During the next year the patient was treated in numerous clinics in the Out-patient Department and was twice admitted to the hospital, once on the Orthopedic Service and once on the Neurological Service. However, the correct diagnosis was not made, she was considered to have psychoneurosis, she became progressively worse, the pains in her hand and back increased, pain in the pubic bones and later generalized bone pain developed, she lost an additional 20 pounds.

The patient again entered the hospital in March 1941. She was not a complete invalid due to her severe bone pains. Further x-rays of the bones and a review of previous films led to the correct diagnosis of Milkman's syndrome.

These x-rays revealed some decalcification of all bones. There were healed fractures of the distal ends of the shafts of the left radius and ulna and of two phalanges of the left hand. The left scapula still showed the pseudofracture previously described. No corresponding fracture was seen in the right scapula. There was an old fracture of the tenth rib on the right. In the pelvis were symmetric pseudofractures radiating from the sacrospinous joints into the ilia, and of the pubic bones running through the superior rami. The skull was only moderately decalcified. The lamina dura was absent about most of the teeth.

Urine analysis showed moderate albuminuria, a specific gravity during a urine concentration test of 1.018, persistently a slight precipitate with Benedict's solution, a urinary pH of 5.5, and many granular and hyaline casts in the sediment. Phenolsulphonphthalein excretion after intravenous administration was 5 per cent in 15 minutes, 7 per cent in one half hour, with a total of 28 per cent in two hours. The studies of the blood revealed 14 gm. of hemoglobin, 4.35 million erythrocytes, 9,300 leukocytes, and a normal smear. Serum analysis showed calcium 9.5 mg. per 100 cc., phosphorus 1.9 mg. per 100 cc., alkaline phosphatase 7.5 Bodansky units, non protein nitrogen 16 mg. per 100 cc., protein 6.9 gm. per 100 cc., CO₂ combining power 16.9 m.eq. per liter, chloride 107.8 m.eq. per liter, total base 158 m.eq. liter, and sodium 138.8 m.eq. per liter. The plasma pH was 7.27. A glucose tolerance test was normal. A tibial biopsy was performed, the bone was decalcified with Mueller's fluid, Dr. Granville A. Bennett did not consider the width of the osteoid seams greater than normal and considered the specimen normal.

On discharge on June 28, 1941 she was given vitamin D₂ 30,000 units daily and 1 sufficient sodium citrate and calcium gluconate to control the acidosis and insure a high calcium intake. Within two months there was a dramatic improvement. By September 1941 the bone pain was decreased, she was able to walk, her appetite had increased, and she was gaining weight. The fractures of the pelvis and right scapula were no longer visible in x-rays taken during January 1942. Serum calcium, phosphorus and phosphatase values returned to normal.

There was persistence, however, of the pain in the third, fourth and fifth fingers of the left hand, this was considered to be a form of neuralgia and in some

was connected with the healed fracture of the radius and a nerve crushing operation of the digital nerves of these fingers was performed by Dr. James C. White in June 1912 following which she was completely asymptomatic for six months. The pain then returned. In March 1913 her left ring finger was amputated which gave complete and permanent relief from this mysterious pain.

The patient continued to be followed in the Outpatient Department. She continued to show a low CO_2 content of the serum and a high serum chloride value when off medication, and normal values when on medication. The latter consisted of large amounts of vitamin D (circa 50,000 units daily) and sodium citrate (circa 2 teaspoonsful of the crystals four times daily). In September 1914 she fell and broke her left arm, this healed without incident.

On December 6, 1944 while asymptomatic, she consented to enter the metabolic ward for the studies discussed elsewhere (see Metabolic Study No. 14, p. 217). This opportunity was taken to check some of the laboratory findings. The urine showed persistent albuminuria which was not orthostatic. The urine sediment was essentially negative. Four urine cultures showed "no growth" and there were no bacteria present in the urinary sediments. (On two occasions in the Outpatient Department, cocci had been present in the urine both in the sediment and on culture, this apparent infection had cleared up with sulfathiazole therapy in spite of the fact that she had taken the drug for only two days.) Her urine reached a specific gravity of 1.018 during a urine concentration test. Renal glycosuria to a very slight degree was probably present, but cystinuria was ruled out. A phenolsulphonphthalein test showed 15 per cent excretion in 15 minutes, 5 per cent in 30 minutes with a total of 30 per cent in one hour. Analyses of the serum showed calcium 10.1 mg. per 100 cc., phosphorus 3.5 mg. per 100 cc., alkaline phosphatase 5.1 Bodansky units, protein 7.8 gm. per 100 cc., chloride 106.0 m eq. per liter, CO_2 content 22.0 m eq. per liter, sodium 137.0 m eq. per liter, and potassium 4.0 m eq. per liter. The blood pressure was 120/80.

Case No. 24: Renal Acidosis, Late Rickets

M. A. (M. G. H. 168199), a 17 year old Canadian born female, first entered the Massachusetts General Hospital on January 7, 1939, complaining of deformities of the legs of 14 years duration.

At 3 bowing of the legs was noticed, at 6 a diagnosis of rickets was made and cod liver oil and sunshine were prescribed, at 10 the patient was studied at the Shriner's Hospital for Crippled Children in Springfield, Massachusetts, where a diagnosis of renal rickets and dwarfism was made and corrective osteotomies were performed, at 13 she sustained a traumatic fracture of the right wrist which healed promptly but with deformity, at 15 her right femur was fractured as a result of trauma and healed in six weeks, but deformities of this leg increased, at 16 she developed a severe pain in the right upper leg and thereafter was unable to walk without crutches. Urinalysis while at the Shriner's Hospital revealed albuminuria and the presence of occasional casts in the sediment, but normal renal function as judged by the phenolsulphonphthalein and urine concentration tests.

The patient had had whooping cough and influenza at the age of 3, mumps at 6 and measles at 12. She had had frequent tonsillitis until a tonsillectomy at 12. Cod liver oil had been administered from early childhood until two years before entry, and she had had ample exposure to sunlight. Catamenia had begun at the age of 15.

The mother and father and six siblings were living and well.

Physical examination except for short stature multiple skeletal deformities characteristic of rickets and a blood pressure of 110/90 was non contributory.

The urine analysis showed moderate albuminuria rare leucocytes in the sediment and a specific gravity of 1.028 during a urine concentration test. Routine blood counts were normal. The serum non protein nitrogen was 33 mg per 100 cc the serum protein 5.0 gm per 100 cc the serum calcium 11.2 and 9.7 mg per

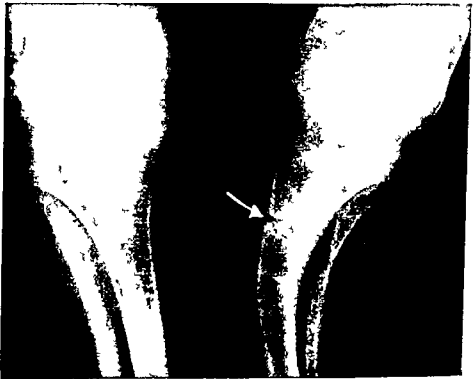


Fig 122 Case No 21 Renal Acidosis Late Rickets X ray Films of Wrist show Pseudofracture (Arrow)

Films taken on 1-13-39 [From Albright Burnett Larson Reifenstein and Roos (1916)]

100 cc on two determinations the serum phosphorus 2.2 mg per 100 cc on each of two determinations the serum alkaline phosphatase 16.3 Bodansky units.

Roentgenographic examination of the skeleton (see Fig 119A and Fig 122) revealed marked generalized changes considered consistent with longstanding rickets. There was a pseudofracture at the upper end of the tibia (see Fig 122). Root formation of the teeth was retarded the lamina dura was thin and in some places completely absent. The distal epiphyseal lines of both radius and ulna showed the characteristic changes of rickets (see Fig 119A). There were multiple old incomplete roughly symmetrical fractures of the femurs tibiae fibulae and metatarsal bones.

The chemical determinations and the x ray findings made the diagnosis of rickets certain, it was felt at that time that the most likely cause of the rickets was a resistance to the usual doses of vitamin D. She was, accordingly, given 120,000 units of vitamin D daily and discharged to the Outpatient Department. An x ray of her right wrist taken 5 weeks later showed the rickets to be healed (see Fig 119B). At this time the serum calcium was 12.5 mg per 100 cc, the serum phosphorus 4.1 mg per 100 cc, serum alkaline phosphatase 14.2 Bodansky units.

Subsequently, her serum CO_2 was found to be 17.8 m eq per liter (normal about 27 m eq). Because of this acidosis and the persistent albuminuria it was felt that some abnormality of renal function might be the basis for her trouble. She was accordingly readmitted for further study on June 26, 1939. Vitamin D had been discontinued on April 22, 1939.

Urine analysis now revealed a pH of 5.5 to 6.0, moderate albuminuria, normal sediment, specific gravity of 1.028 during a urine concentration test and no growth on culture. The excretion of phenolsulphonphthalein after intravenous administration was 10 per cent in 15 minutes, 10 per cent in 30 minutes, 15 per cent in 60 minutes, making 35 per cent in all. The serum chloride was 111.0 m eq per liter, the serum CO_2 content 18.1 m eq per liter, the serum calcium 10.8 mg per 100 cc, the serum phosphorus 3.1 mg per 100 cc, the serum alkaline phosphatase 13.4 Bodansky units. An intravenous pyelogram gave normal findings. The bones of the pelvis appeared more calcified than on the previous examination in January, 1939.

The patient was given large doses of sodium citrate, 25-40 gm daily, for 7 days. On this regime her serum CO_2 rose to 25 m eq per liter, her serum chloride fell to 109.0 m eq per liter, the urine pH rose to 7.5. The patient was again discharged to the Outpatient Department.

Subsequently (most recent visit November 4, 1941) she has remained in excellent health. Most of the time she has taken two teaspoonfuls of sodium citrate crystals dissolved in water three times daily, at times she has taken moderate amounts of vitamin D. In May 1943 she was found to have a normal prothrombin time and normal contents of vitamin A and carotinoid in her blood. Further urine cultures and urine analyses made active pyelonephritis most unlikely.

The pathological physiology and the clinical sequelae resulting from tubular insufficiency without glomerular insufficiency have been presented in a dogmatic fashion. Some experiments on one such patient will now be presented. Before doing this it will be necessary to insert a theoretical discussion.

(1) Digression on Compensatory Mechanisms Which Aid in the Urinary Excretion of an Excess of Acid or Alkaline Radicals

For the understanding of the experimental data to come later the present digression is almost essential. If the intake (diet, medications, etc) contains an excess of inorganic acidic over basic radicals, i.e. an "acid ash" mixture, three chief mechanisms come into play to help excrete the excess acid and so to avoid an acidosis [Gamble, Blackfan, and Hamilton (1925)].

The first and most important mechanism is the production by the kidney



of ammonia. This mechanism requires some time—at least 5 days—to reach its maximum.

The second mechanism is the excretion of an acid urine. As the urinary pH decreases below the neutral point, more and more of the organic acid is excreted free without base and more of the phosphate is excreted in the form of primary phosphate as opposed to secondary phosphate. The saving thus attained is measured by the "titratable-acidity of the urine" which is the amount of base necessary to bring the urine to a pH of 7.4. Since there is a minimum (4.7) to which the pH of the urine can decrease *it is obvious that there is a limit to the titratable acidity depending on this minimum and the amounts of organic acid and phosphate in the urine.*

The third mechanism is the dissolution of bone salts. Of these, the salts other than those of calcium are negligible. Shohl (1939b) states that 85 per cent of the calcium in the skeleton is in the form of tertiary calcium phosphate and 12 per cent in the form of calcium carbonate, this leaves 3 per cent unaccounted for. In the following calculations it will be assumed that this 3 per cent is combined with organic acids such as citric acid. At a pH of 7.4 the tertiary calcium phosphate would be excreted as a mixture of secondary phosphates (80 per cent) and primary phosphates (20 per cent), this would leave 40 per cent ($\frac{1}{3} \times 80 + \frac{2}{3} \times 20 = 40$) of this calcium free for union with other acids. All the calcium of the calcium carbonate and of the calcium salts of other organic acids such as citric acid provided the organic acid radicals are completely oxidized to CO_2 and water, would be available for excretion with mineral acids in the urine. It will be seen, therefore, that 40 per cent of 85 per cent of the calcium dissolved from the bone and 100 per cent of the remaining 15 per cent (49 per cent in all) would be available for neutralizing mineral acids in the urine. To be sure if the urine was acid the calcium dissolved from the bone would have a greater net value but this added value is taken into account in the titratable acidity and so can be dismissed here.

There is a fourth mechanism—the excretion of body fluids, notably extracellular fluids. In the presence of an acidosis the body can excrete some of its fluid and hence make available part of the base of this fluid to neutralize acid. Since most of the base of this fluid is already offset by mineral acids, the actual importance of this source of base is less than one would first think. Furthermore, one cannot keep on excreting body fluids so this mechanism must be considered as a temporary and limited one.

If the intake contains an excess of inorganic basic over acidic radicals, i.e. an 'alkaline ash' mixture, the chief mechanism, as shown by Gamble (1922), relative to the neutralization of the excess of base in the urine is the large amount of carbonate so excreted at alkaline pH's. The concentration of carbonic acid in the urine rests, as does its plasma value, on the

carbon dioxide tension in the alveolar air. Since the hydrogen ion concentration of the urine is determined by the ratio of free carbonic acid to bicarbonate, this fixed value for the numerator prescribes the individual values for bicarbonate over the range of urinary pH's (see Fig 123). The interesting point brought out by Fig 123 is the rapidity with which the bicarbonate in the urine increases as the pH rises above the neutral point.

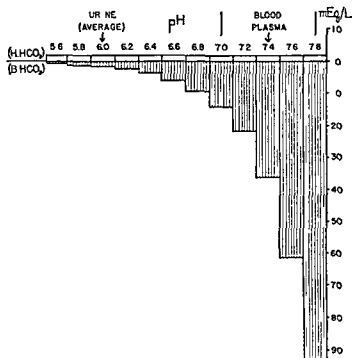


Fig 123 Carbonic Acid and Bicarbonate in Urine

Diagram taken from Gamble (1942) to illustrate the rapid increase in urinary bicarbonate as the urinary pH rises above the neutral point.

The authors are indebted to Dr J I Gamble for permission to reproduce this figure. [From Albright, Burnett, Parson, Reifenstein, and Roos (1946)]

If one knows the pH of the urine and if one assumes a normal tension of carbon dioxide in the alveolar air, one can calculate the amount of bicarbonate in the urine by the Henderson-Hasselbalch equation

$$\text{pH} = 6.1 + \log \text{BHCO}_3 / \text{H}_2\text{CO}_3$$

In Fig 36 of the paper by Albright, Burnett, Parson, Reifenstein, and Roos (1946) some bicarbonate values derived from the above formula are compared with the actual bicarbonate found. All things considered, the agreement is surprisingly good.

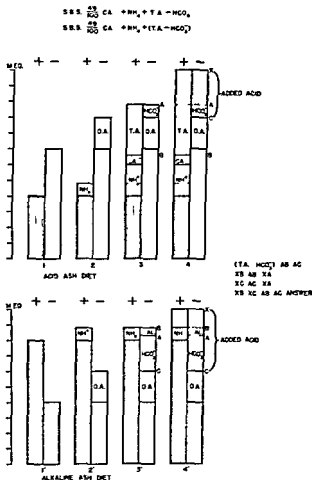


Fig 124 Diagrams to Illustrate 'Acid Ash Diet', 'Alkaline Ash Diet', 'S.B.S.' (Sum of Base Sparers), and 'Titratable Acidity Minus HCO_3^- '

1 Acid ash diet, inorganic (fixed) base is represented by column with vertical lines at left inorganic acid is represented by open column at right difference in heights of columns represents acidity of diet

2 Acid ash diet with corrections on the basic side for that ammonia which is excreted regardless of need for base and on the acid side for the organic acid, it is the difference between the heights of these two columns which must be taken care of by the sum of the base sparsers (S.B.S.)

3 Diagram to represent individual components of S.B.S., namely NH_4^+ , Ca^{++} and Titratable Acidity Minus HCO_3^- . To be strictly correct only that part of the NH_4^+ which is produced in response to the acid regimen over and beyond that which would have been produced regardless of the regimen should be counted, however, since there is no way of separating the two it is best to consider all the NH_4^+ as a part of the S.B.S. As discussed in the text only 49 per cent of the negative calcium balance is counted in the S.B.S.

4 Diagram to illustrate method of computing T.A. minus HCO_3^- as a single value.

From the above discussion it is seen that the ammonia, plus the titratable acidity, plus 49 per cent of the calcium mobilized from the skeleton serve as spacers of base* while the bicarbonate in the urine serves to remove any surplus of base which may have been ingested or which the base spacers may have provided, urinary bicarbonate, therefore, is a negative spacer as it were. This gives us the following quantitative expression for the sum of the base sparing mechanisms (S.B.S.)

$$S.B.S. = NH_4^+ + \text{tit. ac.} + \frac{49}{100} Ca^{++} - HCO_3^-$$

where Ca represents that aliquot of calcium excretion which is derived from the skeleton, namely the negative calcium balance. However, the determination of the titratable acidity and that of the bicarbonate in the urine offer some difficulty due to the ease with which carbonic acid diffuses off. This difficulty can be circumvented by omitting both of these determinations and measuring in their place the 'titratable acidity minus CO_2 ' [Albright, Bauer, Ropes, and Aub (1929)]. This value is obtained by adding a known amount of hydrochloric acid to the urine, aerating until all the CO_2 is driven off, and then titrating back to a pH of 7.4. The answer is obtained by subtracting the amount of acid added from the amount of alkali used in the titration. These steps are illustrated in Fig. 124.

In Fig. 125 some very interesting and pertinent data from a paper by Farquharson, Salter, and Aub (1931) are presented in diagrammatic form†. The data pertain to a man of 37 who was convalescing from lead poisoning and show the effect of various acid and alkaline regimens on the S.B.S. The first point brought out in Fig. 125 is the fairly good parallelism between the S.B.S. and the acidity or alkalinity of the ash of the intake (diet plus medication), it should be noted that the S.B.S. is not zero on a neutral ash diet, this is because of the organic acids which must be covered by S.B.S. Of interest, secondly in Fig. 125 is the insignificance of the calcium mobilized from the skeleton as a factor in the S.B.S. despite the marked increase in the

* By "base" is meant fixed base — i.e. Na, K, Ca and Mg

† The same data were charted in a somewhat different manner by Salter, Farquharson and Tibbells (1933)

From diagram 3 it is seen that $TA - \text{minus} - HCO_3^-$ is represented by the distance AB minus the distance AC. If one adds a known amount of acid (ΔC) to the acid column, thereby setting free the HCO_3^- (AC) it will be seen from the figure that $\Delta B - \Delta C = AB - AC = TA - HCO_3^-$.

1, 2, 3, and 4. These four diagrams represent for an alkaline ash diet the same analyses as diagrams 1, 2, 3, and 4 represent for an acid ash diet. It will be noted that there is no titratable acidity, but in its place titratable alkalinity (TA), titratable alkalinity may be considered as negative titratable acidity, in the arithmetic at the right of the figure. Therefore, the distance BA is considered as the negative distance AB.

excretion during the administration of NH_4Cl (see periods 14 and 15). The third point to be noted is the tendency for the titratable acidity minus-

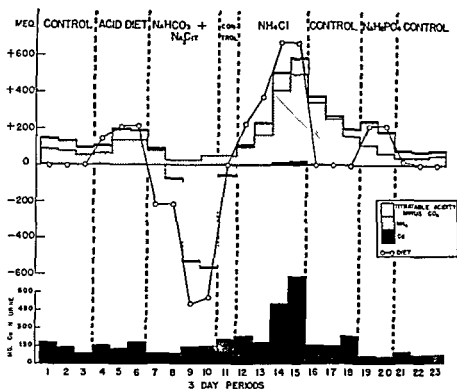


Fig. 125. Comparison of the Acid Values of the Diet with the S.B.S. (Sum of Base Spares) under Neutral, Acid, and Alkaline Regimens.

The base spares—calcium mobilized from skeleton, ammonia, and titratable acidity minus CO_2 —are charted one on top of the other in the order given, where the titratable acidity minus CO_2 is a negative value it is subtracted from the sum of the other two (see periods 7 through 12). The data are charted as 3-day values. In calculating the calcium components of the S.B.S., 49 per cent of the urinary calcium was taken although not all the urinary calcium was necessarily derived from the skeleton; it should be noted that in spite of this the values so charted were insignificant and became detectable in the diagram only during periods 14 and 15. The calcium is charted separately with a larger scale at the bottom to show the marked increase in excretion with ammonium chloride and the failure of the excretion to increase with sodium acid phosphate. For further discussion of diagram see text. [From Albright, Burnett, Parson, Reifenstein, and Roos (1946), the data for this diagram are taken from Farquharson, Salter, and Aub (1931), and are presented here with the permission of the Journal of Clinical Investigation; the authors are indebted to Dr. Harry W. Klinefelter, Jr. for the preparation of this diagram.]

CO_2 to reach a limit on the positive side as discussed above (compare periods 14 and 15 with period 13). Other points of interest in Fig. 125 are the delay in the ammonia excretion in reaching a maximum, the effect of an

increase in phosphate intake on the degree of positivity of the titratable-acidity minus CO_2 (see periods 19 and 20), and, since in a sufficiently acid urine sodium acid phosphate requires no added base, the failure of this salt as compared with ammonium chloride to pull out ammonia or calcium. The last point is all important in the clinical problem of acidifying the urine to prevent the formation of calcium phosphate calculi, but this is aside from the present discussion. Finally, it should be noted in Fig 125 that the S.B.S. did not quite compensate for the increased acidity of the intake when ammonium chloride was added in periods 12 through 15. As had to be the case, this did result in a blood acidosis with a plasma CO_2 content of 14.5 m eq per liter in period 15.

(2) Metabolic Data on Case of Renal Acidosis Resulting from Tubular Insufficiency-Without Glomerular-Insufficiency

Metabolic Study No 14

Case No 23 Renal Acidosis, Milkman's Syndrome

M. St. P. (M.G.H. 237517), a 40 year old white married laundress entered the metabolic ward December 6, 1944. Her clinical history has been given above (see p 237).

A. Experiment A—Effect of Neutral Ash, Acid Ash, and Alkaline Ash Intakes on S.B.S., Calcium Metabolism, and Potassium Metabolism

In Fig 126 are presented some data on Case No 23 obtained during a 33 day study at a time (Dec 1944) when the osteomalacia had been completely cured by previous therapy. She was studied for 12 days on a neutral ash diet for 5 days on an acid ash regimen (neutral ash diet plus 130 m eq of ammonium chloride by mouth per 24 hours) for 7 days back on the neutral ash diet, and finally for 9 days on an alkaline ash regimen (neutral ash diet plus 350 m eq of sodium lactate per 24 hours by mouth). For a considerable period before the onset of the investigation and throughout the entire investigation, the patient received 50,000 units of vitamin D daily, this insured an adequate calcium absorption and precluded any changes in calcium metabolism resulting from fluctuations in the ultra violet light in the atmosphere. On day 17, the last day of the ammonium chloride administration, the patient developed pain in her arms which is often the first symptom of the low potassium syndrome and for four days thereafter was unable to eat all her diet; this explains the decreased intakes during days 18 through 21.

Serum chloride and serum CO_2 content. At the top of Fig 126 it will be seen that during the 12 days on the neutral ash regimen the serum chloride and serum CO_2 content were within normal limits, that with the administration of ammonium chloride the serum chloride rose to a high level (112 m eq per liter) and the CO_2 content fell to a low level (13.0 m eq per liter), that during the control days back on the neutral ash regimen these values returned to normal, and that finally, with the administration of sodium lactate, there was a further slight rise in CO_2 content.

Comparison of S.B.S. with acidity value of ash intake. Note in Fig 126 as in

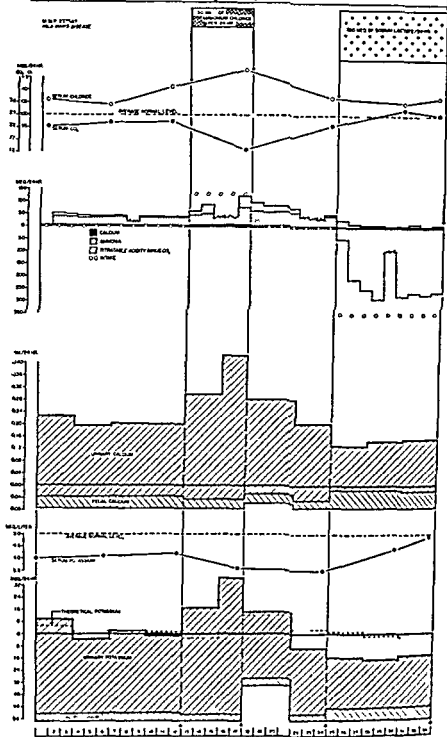


Fig 126 Experiment A, Case No 23, Renal Acidosis and Cured Milkman's Syndrome Comparison of the Effect of a Neutral Ash Regimen with an Acid Ash Regimen and an Alkaline Ash Regimen

For discussion see text [From Albright, Burnett, Parson, Reifenstein, and Roos 1958]

Fig 125, that the calcium component of the S B S is negligible throughout, that, as in Fig 125, the S B S has an appreciably positive value to offset the organic acids during the neutral ash regimen (see days 1 through 12), that with the administration of ammonium chloride the S B S does not rise as much as the acidity value of the intake which makes a blood acidosis a necessary sequel, that with the omission of ammonium chloride the S B S continues high (days 18 through 21) until the acidosis is dispelled (day 24) and, finally that with the administration of sodium lactate the S B S becomes a negative value but not quite so negative as the acidity of the regimen, presumably because of the continued presence of organic acid in the urine. Indeed, the discrepancy between the acidity of the regimens and the S B S is greater with the alkaline regimen than during the neutral regimen, this suggests an increase in organic acid excretion during the alkaline regimen which is what one would expect. The important point for the argument at hand, however, is the fact that the S B S, while definitely rising does not rise sufficiently to compensate for the 130 m eq increase in acidity during the administration of ammonium chloride, this speaks for an impaired tubular function as hypothesized above. In Fig 127 (vide infra) these data will be compared with those from a normal individual who received the same amount of ammonium chloride. The "normal individual" in Fig 125 received 224 m eq of ammonium chloride daily instead of 130 m eq so the data on him cannot be used in comparison.

Calcium metabolism It will be noted in Fig 125 that the calcium metabolism behaves in accordance with the hypothesis outlined above. Thus during the neutral ash regimen (days 1 through 12) there is a large amount of calcium in the urine and a large negative calcium balance, with the ammonium chloride administration there is a sharp rise in the urinary calcium excretion, with the omission of ammonium chloride there is a return to the initial level of calcium excretion, and, finally with the administration of sodium lactate there is a definite fall in the urinary calcium excretion. As in Fig 125 the parallelism between the ammonia and the calcium excretions in the urine should be noted.

Potassium metabolism In the potassium metabolism data at the bottom of Fig 126 note that urinary excretion parallels the urinary calcium excretion very closely. Thus, during the neutral regimen there is potassium equilibrium, with the administration of ammonium chloride there is a sharp increase in the urinary potassium excretion and a fall in the serum potassium level, with cessation of the ammonium chloride administration there is a lowering in the urinary potassium excretion, finally, with the administration of sodium lactate there is a strongly positive potassium balance and a rise in the serum potassium level. The theoretical potassium balance, by which is meant the balance which one would calculate on the assumption that the potassium balance is dependent on the amount of protoplasm ($1 \text{ gm N} \approx 2.7 \text{ m eq K}$) formed or destroyed, is most instructive (see dotted line). It will be noted that, with the administration of ammonium chloride, the actual potassium balance becomes strongly negative while the theoretical balance remains unchanged. This is an indication that the potassium loss during acidosis is not due to destruction of protoplasm. It will be further noted that with the administration of sodium lactate there is a strongly positive actual potassium balance while the theoretical potassium balance remains essentially zero.

B Experiment B—Effect of 130 m eq of Ammonium Chloride Daily on Patient with Renal Acidosis Compared with Effect on a Normal Individual.

The thesis under investigation holds that the individual with this special type of renal acidosis cannot compensate for an excess of acid in the intake as effectively as a normal individual. It was therefore important to study an individual with renal acidosis and a normal individual under conditions as nearly the same as possible. This was done and the data are shown in Fig. 127. The data on the right side of Fig. 127 are the same data as shown for days 10 through 17 in Fig. 126 (Case No. 23). The data on the left side of Fig. 127 represent the corresponding data for the normal individual [L. C. (M. G. H. 438193), a 22 year old white male]. Both individuals ate the same neutral ash diet except that the normal individual, having a somewhat greater energy output, received 20 per cent extra of each component of the diet. Both individuals received 130 m eq. ammonium chloride for five days. Charted in Fig. 127 are three control days on the diet alone followed by five days of ammonium chloride administration. The most important feature of the experiment concerns the changes in ammonia and titratable acidity minus CO_2 as a result of the administration of ammonium chloride, whereas both individuals had a marked increase in both of these factors, in the normal individual the combined increase (118.6 m eq. on 5th day of ammonium chloride administration) almost offset the increase in acidity (130 m eq.) whereas in the patient with renal acidosis the combined increase (77.0 m eq.) on the 5th day of ammonium chloride administration fell far short of this. Consequently, the serum chloride, CO_2 content, and pH in the normal individual showed no significant changes; in the patient with renal acidosis on the other hand there was a marked rise in the serum chloride and a marked fall in the serum CO_2 content and in the serum pH. The calcium excretion in the normal individual rose slightly, in the patient with renal acidosis it rose markedly. Finally, there was no change in urinary potassium excretion in the normal individual, whereas there was a marked increase in the patient with renal acidosis accompanied by a fall in the serum potassium level.

Case No. 25 Renal Acidosis, Nephrocalcinosis, Pyelonephritis (*Staph. Albus* and *B. Coli*), Chemical-Osteomalacia-Without High Phosphatase, Decreased Stature

A. S. P. (M. G. H. 311058) a single woman of 28, entered the hospital on July 15, 1911 complaining of bilateral pain in the region of the kidneys, dysuria, hematuria, and the passage of gravel of about four months duration. Frequency and nocturia had started about four years previously and she had first developed bilateral flank pains one year previously following a cold.

In her past history, she had always been rather sickly and had had the usual childhood diseases including scarlet fever. Of especial interest as it suggests a low serum potassium is the history of paralysis of the arms and legs of 3 days duration about 8 years previously which disappeared spontaneously.

Physical examination was non-contributory except for very short stature blood pressure was 130/80.

Laboratory studies: urine—slight albuminuria, slight pyuria, hyposthenuria (specific gravity 1.010 during a concentration test), phenolsulphonphthalein excretion 10 per cent in 15 minutes and 40 per cent in one hour, urine culture—*Staphylococcus albus* and *B. coli*, serum chemistry—calcium 9.7 mg. per 100 cc., phosphorus 2.2 mg. per 100 cc., alkaline phosphatase 4.8 Bodansky units, CO_2 combining power 18 m eq. per liter, chloride 117.0 m eq. per liter, protein 6.6 gm.

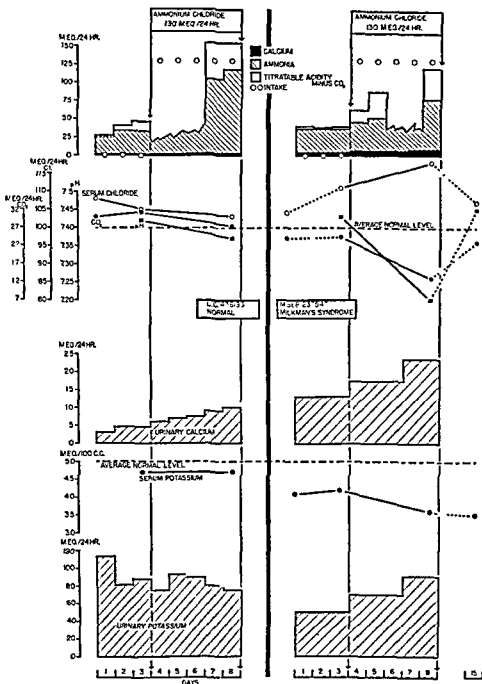


Fig 127. Experiment B, Case No. 23, Renal Acidosis and Cured Milkman's Syndrome. Comparison of the Effect of 130 mEq of Ammonium Chloride on a Normal Individual and a Patient with Renal Acidosis

For discussion see text. (From Albright, Burnett, Parson, Reifenstein, and Roos (1916))

prothrombin time normal, analysis of the stones—strongly positive test for phosphorus and negative tests for uric acid and oxalate

X rays showed generalized demineralization, poor calcification of both osteotomy calluses at lower ends of the femurs (see Fig 120B), bilateral nephrocalcinosis (see Fig 115D), stones at the lower end of the right ureter (see Fig 121A) scoliosis of the spine, narrowing of the pelvis, coxa vara deformities of the upper ends of the femora united but uncalcified fractures in the pubic bone (see Fig 121A), multiple similar fractures of the ribs symmetrical fractures of the surgical necks of both humeri and moderately well preserved lamina dura

The patient received large amounts of alkali (sodium citrate 1 teaspoonful 4 times daily), large amounts of vitamin D [circa 3 mg (120 000 units) of vitamin D₃ daily] and a goodly amount of calcium in the form of milk Her skeleton responded very well (see Fig 121) and she walked out of the hospital on July 28, 1943 approximately 4 months after entering On March 3 1945 the serum calcium was 9.0 mg per 100 cc, the serum phosphorus 2.9 mg per 100 cc and the serum alkaline phosphatase 3.5 Bodansky units

Case No 27 Renal Acidosis, Hypokaliëmic Syndrome, Chemical Osteomalacia

The first two admissions, in October and November of 1943 respectively, of J. J. F. (M.G.H. 424073), a married man of 40 were to the Neurological Service for symptoms which were finally diagnosed by Dr. K. P. Bird on the second admission as being due to hypokaliëmia [see Brown, Currens and Marchand (1944)] On October 13 1943 two days before his first admission, the patient noted weakness of his left leg with pain in the muscles, there was also some back pain, on the following day his arms and legs became paralyzed—the left more than the right The symptoms were improved by prostigmine Neurologic examination was non contributory except for a Horner's syndrome on the right A lumbar puncture revealed no abnormalities in the spinal fluid The symptoms rapidly cleared up after admission to the hospital and he was discharged without a definite diagnosis having been arrived at on October 26 1943 He entered the hospital again with essentially the same symptoms and findings on November 11, 1943

In his past history, he had had a penile lesion, a urethral discharge and an epididymitis at 20, a traumatic hematuria at 25, ureteral colic with passage of gravel at 38, and a recently acquired alcoholism with morning vomiting and loss of weight

Physical examination was non contributory except for the findings associated with hypokaliëmia His blood pressure was 112/80

Laboratory studies urine—moderate albuminuria, slight pyuria no glycosuria, marked hypercalcaemia as shown by Sulkowitch tests fixation of pH at 6.5 to 7.0, specific gravity of 1.018 during a urine concentration test, phenolsulphonphthalein excretion excellent (40 per cent excretion in the first 15 minutes, 80 per cent in 2 hours), serum levels (some of the following at a later date)—potassium 2.5 m eq per liter (normal circa 5 m eq per liter), calcium 8.8 mg per 100 cc, phosphorus 2.7 mg per 100 cc, phosphatase 5.5 Bodansky units, sodium 141.0 m eq per liter, chloride 110.0 m eq per liter, CO₂ content 18.8 m eq per liter, total protein 6.0 gm per 100 cc, non protein nitrogen 24 mg per 100 cc, red count 5.1 million, white count 9,700 analysis of the calculi—a strongly posi

tive test for phosphate and a very weak test for oxalate, repeated specimens for urine culture—no organisms in the smear, *Staphylococcus* on culture of most of the specimens, Hinton test for syphilis negative, electrocardiograms—low T wave characteristic of hypokalemia and a reversion to a normal tracing after the latter condition was corrected

X rays showed normal density of the skeleton, bilateral renal calculi, and rather poor dye excretion by the kidney

The diagnosis of renal acidosis resulting from tubular insufficiency without glomerular insufficiency with a complicating hypokalemia and possibly a pyelonephritis was made. In addition he had chemical osteomalacia with high phosphatase. Accordingly he was started on one teaspoonful each of sodium citrate, potassium citrate, and calcium gluconate daily. On this regimen the pH of his urine rose to 7.5, the serum CO_2 content rose to normal and the serum chloride fell to normal, the serum phosphorus rose and the serum phosphatase fell. Calcium disappeared from his urine, the albuminuria also disappeared.

Later, because of the possibility of an underlying, low grade pyelonephritis he was given a course of penicillin therapy. The urine culture became negative during this therapy but later reverted and it is questionable whether this therapy had any permanent effect. Following this course of therapy he was taken off alkali; this was followed by another attack of hypokalemia, a recurrence of hypercalcuria and albuminuria, and the passage of more stones. The patient went back on alkali and these findings again cleared up.

Case No. 28 Renal Acidosis, Osteomalacia, Hypokaliemia, Nephrolith

17515

The patient, M. B. (M. G. H. 202252), a single girl of 23, entered the Massachusetts General Hospital on the Arthritic Service in August, 1939, complaining of back trouble*. She traced the onset of her illness to a ride in a roller coaster two years previously following which she developed pain in her back. The pain spread to her hips and she developed a limp. She was not improved by therapy prescribed by a chiropractor, crutches were tried for 8 weeks without benefit. Later she became very weak and lost weight.

Her past history was irrelevant except for passage of gravel in her urine at the age of 10.

On physical examination the pertinent findings were undernutrition, a stiff back which led to the diagnosis of spondylitis, and a blood pressure of 120/70.

Laboratory studies: urine—albumen ++, specific gravity 1.001 to 1.012, pyuria; urine culture—no growth, serum chemistry—non protein nitrogen 25 mg per 100 cc, calcium 9.7 and 10.1 mg per 100 cc, phosphorus 2.8 and 2.2 mg per 100 cc, alkaline phosphatase 8.4 and 9.2 Bodansky units, sodium 145.0 and 142.0 m eq per liter, chloride 117.0 m eq per liter, CO_2 combining power 20.0 m eq per liter, protein 8.6 gm per 100 cc, red count 4.5 million, hemoglobin 80 per cent of normal, white count 7,200.

By x ray the spine was remarkable only in that the dorsal spine was straight and that there was a slight scoliosis in the lumbar region, the right twelfth rib

* The authors are indebted to Dr. William Beckman for bringing this case to their attention and for permission to use it.

showed a transverse fracture line with callus formation (see Fig 128), a similar fracture was present in the right scapula (see Fig 128B) but was not noticed at the time, there were stones in the left kidney, an intravenous pyelogram confirmed the stones in the left kidney and showed a good functioning right kidney and a rather poorly functioning left kidney a retrograde pyelogram failed to show hydronephrosis on the left

With the albuminuria pyuria high serum chloride low serum CO_2 low serum phosphorus and high serum phosphatase it is now easy in retrospect to make the diagnosis of osteomalacia secondary to renal acidosis

This diagnosis however was not made and the patient was given three liters

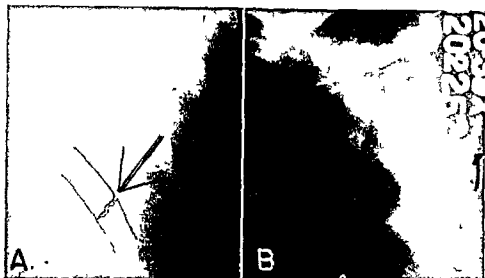


Fig 128 Case No 28 Renal Acidosis, Milkman's Syndrome X ray films of Scapula and Ribs to Show Pseudofractures

Note fracture lines in right scapula and right twelfth rib (arrows) Note good density of bones in spite of florid osteomalacia [From Albright Burnett Pearson, Reifenstein and Roos (1946)]

of 5 per cent dextrose in normal saline on September 4 a liter and one half of normal saline on September 5 and the same amount again on September 6 As demonstrated by Albright Consolazio Coombs Sulkowitch and Tallott (1946) the taking of NaCl increases an acidosis such as this one secondary to tubular insufficiency and to be sure, this patient's condition did grow rapidly worse On September 8 the record states that "motion and strength in extremities is normal at times but patient complains of great weakness—even paralysis—much of the time", it goes on to state that patient calls nurses incessantly to move her head her arms or her legs These bizarre symptoms were almost certainly due to a low serum potassium unfortunately no potassium determination was made The following day the patient became stuporous and was seen by Dr William Beckman who advised parenteral alkali therapy but she died before this was given The chemistry of her serum taken shortly before death showed chloride 128 m eq per liter, CO_2 combining power 13.0 m eq per liter, sodium 151 m eq

per liter, protein 8 gm per 100 cc, calcium 9 mg per 100 cc, phosphorus 1.5 mg per 100 cc, and alkaline phosphatase 8.2 Bodansky units

It is clear, therefore, that the acidosis had markedly increased, presumably due to the saline intravenously. It is not unlikely that the patient had terminally a very low serum potassium level and that this accounted for the symptoms suggesting paralysis; unfortunately, no potassium determination was done.

Autopsy showed nephrolithiasis, chronic pyelonephritis, parathyroid hyperplasia, florid osteomalacia (see Fig 129), and acute necrosis with question of infarction of the pons.



Fig 129 Case No 28, Renal Acidosis, Osteomalacia. Photomicrograph of Vertebral Changes at Autopsy to Show Osteoid Seams.

Note that the trabeculae are surrounded with osteoid (os) which prevents any calcified matrix (c.m.) from reaching the surface. [From Albright, Burnett, Parson, Reifenstein, and Roos (1916)]

Since the kidney pathology is thought to be the primary factor in the syndrome under discussion, the kidney findings are reported in more detail.* The right kidney weighed 275 gm and the left 150 gm, the capsules stripped with some difficulty, the cortices measured 5 mm in thickness, the pelvis were negative; there were two stones lying free in the calices of the left kidney. On microscopic examination the majority of the glomeruli seemed normal, where pathology was present it varied from capsular thickening to complete fibrosis of the capillary

* The authors are indebted to Dr. Marshall D. Ruffin for the gross autopsy findings, and to Dr. Ronald C. Sniffen and Dr. Benjamin Castleman for the microscopic findings in the kidneys.

tuft. The tubules were damaged most severely in their proximal and distal convoluted portions: the cells of the convoluted loops were swollen, finely granular, and contained vacuoles and an occasional hyaline droplet in the cytoplasm. There were a few large groups of dilated tubules lined with atrophic epithelium and filled with so called 'colloid crsts'—findings characteristic of chronic or healed pyelonephritis. The interstitial tissues showed patchy infiltration with polymorphonuclear neutrophils and eosinophiles, lymphocytes and plasma cells. The blood vessels were not remarkable except for an occasional thickened arteriole. The most impressive change was the vacuolization in the convoluted tubules, especially the distal portions which, because of its extreme degree and the accompanying granularity, was thought not to be a post mortem change. The latter could not definitely be ruled out.

(F) *Renal Acidosis of the Fanconi Syndrome Type—Aminodiabetes*,
Hyperaminoaciduria

The authors have had no personal experience with late rickets or osteomalacia resulting from the Fanconi syndrome: their remarks are based largely on the excellent review by McCune, Mason and Clarke (1913) and a few of the key papers.

Fanconi (1936) described a syndrome characterized by an hereditary tendency often accompanied by a family history of consanguinity, impaired growth beginning at an early age, rickets, albuminuria, renal glycosuria, a persistently alkaline reaction to the urine, an increase of organic acids, ammonia, phosphorus and calcium in the urine, a marked hypophosphatemia without hypercalcemia, a lowering of the blood bicarbonate without azotemia, and degenerative changes in the renal tubular epithelium. Fanconi very astutely ascribed the condition to an anomaly of the structure and function of the tubular portion of the kidneys whereby the tubular epithelium fails to resorb certain solutes from the glomerular filtrate. This interpretation has been generally accepted by later investigators, notably McCune, Mason and Clarke (1913), who have further extended it, albeit in a somewhat modified form (*vide infra*). The latter authors confirmed the high excretion of organic acids and found that 82 per cent were amino acids, 11 per cent lactic acid, and seven per cent beta-hydroxybutyric acid. The renal glycosuria, the hyperaminoaciduria, and the hyperphosphaturia with resulting hypophosphatemia, they explain on decreased reabsorption in the tubules; they go on to point out that, 'inasmuch as the absorption of dextrose is mediated through the formation of phosphate esters such an assumption supplies a speculative nexus between the glycosuria and the hyperphosphaturia'. As another possible cause for the hyperphosphaturia, McCune, Mason and Clarke (1913) mention a secondary hyperparathyroidism (*vide infra*). The rickets, of course, they ascribe to the hypophosphatemia: be its cause what it will. The excess of beta-hydroxybutyric acid in the urine they explain by the

hypoglycemia resulting from the renal glycosuria. Fanconi (1946) attributes the hyperaminoaciduria to a disturbed oxidative deamination in general, so that besides amino acids there are found in excess also amines, to the presence of the latter in the urine he ascribes the alkalinity. However, an alkaline urine, one of the features of Fanconi's cases, has not been a constant finding in subsequent cases. Fanconi suggested the name, "amindiabetes."

Beumer and Wepler (1937) pointed out the similarity in many respects between the Fanconi syndrome and cystinosis, and suggested a common or related etiology. This was confirmed at autopsy by Fanconi (1946) for one of his cases. A detailed report of the autopsy was published by Looser (1944) together with an analysis of ten cases from the literature. He found cystine deposits in almost all organs—notably lymph nodes, spleen, liver, and kidneys. These deposits were mostly in the reticulo-endothelial system. He pointed out that, by and large, cases with cystine deposits do not have cystinuria and vice versa. Deposits occur only when there is a combination of a primary disturbance in cystine metabolism plus a secondary inability on the part of the kidney to excrete it. The presence of cystine deposits (cystinosis) can readily be demonstrated by sternal puncture.

The pathologic physiology of the disturbed amino acid metabolism in an adult patient with a disorder most suggestive of an adult form of the Fanconi syndrome was clarified by the studies of Dent (1946) in which he employed a new method (partition chromatography on paper) of identifying and roughly quantitating amino acids and other related substances in urine. His studies were carried out on a man of 34 with skeletal symptoms, who showed by x-ray pseudofractures and the characteristic skeletal deformities of osteomalacia. Important laboratory findings were glycosuria without hyperglycemia, elevated ammonia nitrogen coefficient of urine, elevated alkaline phosphatase level in the serum, normal serum calcium level (11.3 mg per cent), low plasma inorganic phosphorus level (1.8 mg per cent), and normal serum amino nitrogen level. While under observation the patient developed portal obstruction due to an underlying cirrhosis which eventually led to his death. At autopsy no cystine was found in any of his organs.

Dent observed that the blood level of amino acids was not elevated but that the renal threshold for amino acids was lowered. As a result excessive amounts of amino acids appeared in the urine (circa 1000 mg amino acid nitrogen per 24 hours) and caused a high ratio of amino acid nitrogen to total nitrogen in the urine (circa 10 per cent, normal 1-2 per cent). The hyperaminoaciduria was independent of the protein intake and the clinical state of the patient. It bore a direct relationship to the glycosuria but

not to the phosphaturia. Also as a result of the lowered threshold, amino acids normally present in blood escaped into the urine in sufficient quantities to be identified. Thus, all of the 20 common amino acids occurring in protein except tryptophane and lysine, several uncommon amino acids including citrulline and α amino n butyric acid, and a peptide (seryl glycl glycine) were found at one time or another. He did find, however, that the excretion of the amino acids containing hydroxyl groups (serine, threonine, seryl glycl glycine, and tyrosine) was increased out of proportion to that of the other amino acids. The excretion of cystine was not excessive.

Dent differentiates two forms of hyper aminoaciduria "overflow" (as in acute yellow atrophy), and 'renal' (as in the Fanconi syndrome). In the first the blood amino acid levels are high and the renal amino acid threshold is normal, in the second the blood levels are normal and the renal threshold is low.

In summary, there seem to be several different patterns to the disordered amino acid metabolism in late rickets or osteomalacia of the Fanconi syndrome type, furthermore, these different patterns tend to blend more or less with one another. Thus, there may be hyper aminoaciduria without a disproportionate increase in cystine in the urine and without cystine deposits (Dent's case and McCune, Mason, and Clarke's case), then, there may be cystinuria without cystine deposits and cystine deposits without cystinuria, both with more or less hyper aminoaciduria in general.

The subject is further complicated by 'hereditary cystinuria' where one finds renal calculi of pure cystine and marked cystinuria but no rickets. Dent (1946) has studied the urinary amino acid partitions in three such cases and found, in addition to the increased cystine, large amounts of arginine and citrulline, but no increase in the two amino acids which normally appear in the urine (glycine and alanine). The presence of amino acids other than cystine in excess in the urine in this condition has been confirmed by Dr. Frederic C. Bartter in our laboratory. It is quite clear, therefore, that the derangement in amino acid metabolism involves several amino acids other than cystine; the latter has come into prominence only because of its insolubility which leads to calculi formation in the urinary passageways or deposits in the tissues.

It would appear that the tubular acidosis associated with the Fanconi syndrome is entirely different from the tubular acidosis discussed in the preceding section. Thus, in the Fanconi syndrome the acidosis may be due to increased urinary excretion of base secondary to the increased urinary excretion of organic acid, in the other syndrome the acidosis is due to a decreased ability of the kidneys to make ammonia and to excrete an acid urine. Therefore, one would expect increased organic acids, increased

ammonia and increased titratable acidity in the urine in the Fanconi syndrome, normal amounts of organic acids, decreased ammonia and decreased titratable acidity in the urine in the syndrome discussed in the preceding section, and an increased calcium in the urine in both syndromes. In Table 6 a comparison is made between the findings in Case No. 24 and those in the case reported by McCune, Mason, and Clarke (1943). It will be seen that the findings were as expected.

As discussed above, McCune, Mason and Clarke (1943) interpret the data to indicate diminished ability of the tubular epithelium to resorb dextrose, amino acids, and phosphates, but point out as an alternative possibility that the hyperphosphaturia may be the result of a secondary hyperparathyroidism. In Fig. 130 is depicted a possible interpretation of the inter relationships in the disordered homeostasis in the Fanconi syn-

TABLE 6

Findings in Case No. 24 with Renal Acidosis Resulting from Tubular Insufficiency Without Glomerular Insufficiency Contrasted with Findings of Patient with Fanconi Syndrome Reported by McCune, Mason, and Clarke (1943)

Condition	Serum		Urine			
	Cl	CO ₂	pH	$\frac{\text{Ammonia}}{\text{Tot. N}} \times 100$	Titr. Ac.	Organic Acid
	<i>meq / liter</i>	<i>meq / liter</i>			<i>meq / kg / 24 hr</i>	<i>meq / kg / 24 hr</i>
Normal	104	27	4.5-7.5	4	0.20-0.80	1
Renal acidosis, Case No. 24	113	17	6.4-6.5	7	0.12-0.29	1
Fanconi syndrome case of McCune <i>et al.</i> (1943)	104	19	4.8-6.8	24	1.20-2.50	10

drome, Fig. 130 is to be compared with Fig. 117, p. 232, a similar diagram for the other type of renal acidosis leading to late rickets or osteomalacia. In Fig. 130 the hyperphosphaturia is ascribed to a secondary hyperparathyroidism although the first explanation of McCune, Mason, and Clarke has much to recommend it.

As regards treatment, McCune, Mason, and Clarke came to no definite conclusion. The authors would anticipate that the osseous disorders would respond to the same measures as used for the other type of renal acidosis, namely, alkali, plus high calcium intake, plus vitamin D. For theoretical reasons, a very high phosphate intake should be tried.

(G) *Osteomalacia Resulting from Hypercalcuria Without Hypercalcemia and Without Renal Acidosis ("Idiopathic Hypercalcuria")*

There seems to be a not inconsiderable number of cases wherein the primary defect in metabolism is a propensity on the part of the kidneys to

excrete an increased amount of calcium for any given level of calcium in the serum. Such, to be sure, is the finding in those cases secondary to renal acidosis (*vide supra*). However, the cases under discussion do not have an acidosis, and the calcium excretion in the urine, in contrast to the finding in cases with acidosis, is not decreased by alkali therapy (see Fig 111, p 220). The sequence of events in the disordered homeostasis is the same as in vitamin D lack (see Fig 65, p 133) except that the first step, instead of being decreased calcium absorption, is increased-calcium-excretion, the

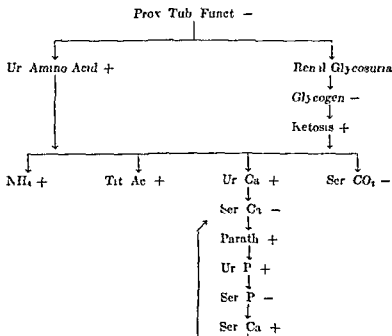


Fig 130 Diagram of Disordered Homeostasis in Fanconi Syndrome

Compare with Fig 117 [From Albright Burnett Parson Reifenstein and Roos (1916)]

second step in both sequences is the same, tendency to low serum-calcium level. As one might anticipate, the increased calcium excretion in the urine favors kidney stone formation and it is in the Stone Clinic that most of these cases are found. Indeed, of the following four metabolic disorders leading to increased urinary calcium excretion—hyperparathyroidism, osteoporosis during the stage of progression, renal acidosis, and idiopathic hypercalcaemia, it is the last of these which is probably the most common and accounts for the finding of Flocks (1910) that hypercalcaemia is very common in patients with kidney stones. Few cases proceed to a greater degree of osteomalacia than "chemical-osteomalacia without high phosphatase

But the authors have one case with kidney stones who has 'chemical-osteomalacia with high phosphatase' and one case, other than the one whose data are presented in Fig 111 p 220 who has out-and-out-osteomalacia. The bone condition responds to a high calcium high vitamin D regimen often however, this is contra indicated because of the nephrolithiasis.

Many of these cases have or have had *Staphylococcus* pyelonephritis whether this is the cause or the result of the condition has not yet been established. Mention has already been made (see p 34) of the occasional

TABLE 7

Summary Table of Laboratory Tests in Different Types of Osteomalacia

Condition	Serum					Urine				Serum Ca nolds	Vit A&K Tests
	Alk P t se	Ca	P	CO ₂	Cl	Ca	NH	Tit Ac	Sug Acet		
Simple vitamin D lack	H*	N or L	L	N	N	L	N	N	0	N	N
Resistance to vitamin D	H	N or L	L	N	N	L	N	N	0	N	N
Steatorrhea	H	N or L	L	N	N	L	N	N	0	I	I
Renal acidosis (tubular in sufficiency without glo- merular insufficiency)	H	N or L	L	L	H	H	L	L	0	N	N
Renal acidosis (Fanconi syn- drome)	H	N or L	L	L	N	H	H	H	+	N	N
Idiopathic hypercalcaemia	H	N or L	I	N	N	H	N	N	0	N	N
Ost fib gen after removal of parathyroid tumor	H	L	L	N	N	L	N	N	0	N	N

* N = normal L = low H = high + = present

occurrence of hypercalcaemia in the presence of a low serum calcium level in patients with hypoparathyroidism and urinary tract infections.

(H) *Osteomalacia Following Removal of Parathyroid Tumor in Osteitis Fibrosa Generalisata*

This transient and rare, but academically interesting form of osteomalacia has been discussed in Chapter 3 (see p 104).

VI DIFFERENTIAL DIAGNOSIS OF ETIOLOGICAL SUB-GROUPS OF OSTEOMALACIA

The points in the differential diagnosis of the seven causes for osteomalacia discussed in this Chapter are shown in tabular form in Table 7.

CHAPTER 8

POLYOSTOTIC FIBROUS DYSPLASIA (OSTEITIS FIBROSA DISSEMINATA)

I MORBID ANATOMY

In the first communication from this clinic [Albright, Butler, Hampton, and Smith (1937)] on this bizarre syndrome, its triad of abnormalities was listed as follows: "(A) bone lesions which have a marked tendency to be unilateral and which show osteitis fibrosa on histologic examination (B) brown non elevated pigmented areas of the skin which tend to be on the same side as the bone lesions, and (C) an endocrine dysfunction which in females is associated with precocious puberty."

(A) Skeletal Manifestations

The skeletal abnormalities are spotty in distribution and consist of multiple localized lesions with normal bone elsewhere. In many instances they show a tendency to be unilateral, in almost all they are segmental in their grouping. Thus, they will involve multiple bones in one extremity or one digit, and entirely miss the other extremity or another digit (see Fig. 131 and 132). There are certain sites of predilection, the occiput, the metatarsals and metacarpals, the phalanges, the upper ends of the femora and the tibiae. On the other hand, the epiphyses of the phalanges, metatarsals, and metacarpals usually, but not always, escape involvement (see Fig. 133). The most common grouping comprises unilateral involvement of one leg with lesions of the ilium, of the head and neck of the femur, of the tibia, and of the metatarsals and phalanges of one or two toes (see Fig. 134).

The roentgenographic appearance of the bone lesions is only superficially suggestive of that seen in hyperparathyroidism. An important difference is the presence of lesions of increased density in addition to the areas of decreased density (see Fig. 135). The base of the skull is especially prone to be very dense and hyperostotic (see Fig. 136), this may lead to proptosis of one or both eyes. A marked prominence in the region of the occiput has been observed in several cases (see Fig. 137 A and B). There is no generalized decalcification and the lamina dura, if not directly involved in a bone lesion, should be intact.

Pathological fractures are common and usually heal well. The upper ends of the femora, when involved, usually result in outward bowing (the "shepherd-crook deformity", see Fig. 145), this leads to a bad mechanical set up with recurring fractures and pseudoarthroses and constitutes one

of the most troublesome complications of the syndrome (see Fig 141 A, B, C)

The involved bones, on histological examination, show the characteristic findings of osteitis fibrosa (see Fig 138) except that one occasionally finds islands of cartilage (see Fig 139) In some cases it is quite clear that these islands have arisen from epiphyseal cartilage (see Fig 139A) This suggests, of course, that the syndrome has some of the elements of a dyschondro-

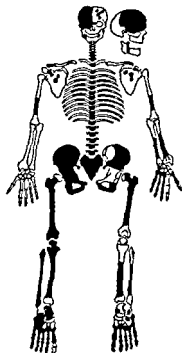


Fig 131 Distribution of Bone Lesions in a Case (M G H 328005) of Polyostotic Fibrous Dysplasia

Note that all fingers of right hand escape involvement while all fingers of left hand are involved except for the index finger which entirely escapes (cf Fig 132) [From Albright, Butler, Hampton, and Smith (1931)]

plasia that this is not the entire explanation is shown by the fact that the vaults of the skull, membranous bones are very often involved

In those female patients who develop precocious puberty (*vide infra*) the bone age is likewise precocious

(B) Cutaneous Pigmentation

The second feature of the syndrome is the pigmentation This consists of small or large, irregular *café-au lait* areas which have a segmental distribution roughly similar to that of the bone lesions In one case the

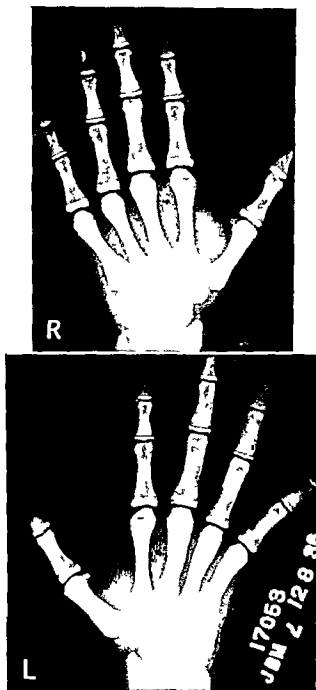


Fig 132 X Ray Film of the Hands of a Case (M G H 358005) of Polyostotic Fibrous Dysplasia to Show Distribution of Bone Lesions

Note that bones of all fingers of the right hand are normal whereas bones of all fingers of the left hand are involved except for those of the index finger which escapes entirely (cf Fig 131) [From Albright Butler Hampton and Smith (1937)]

mucous membranes of the mouth were also involved. The pigmentation tends to be lighter in color than that seen in neurofibromatosis, furthermore, the edges of the areas of pigmentation are less regular than in that disease. Thus, in our clinic we differentiate, according to their contours, two types of pigmentation, viz 'coast-of Maine' pigmentation found in the syn-



Fig 133 Polyostotic Fibrous Dysplasia X ray Film of Hand to Show Bone Lesions

Note that all bones are involved except epiphyses and carpal bones (Patient A C Children's Hospital 177569)

drome under discussion and the 'coast-of-California' pigmentation of neurofibromatosis (see Fig 140 and 142). The pigment is melanin.

(C) *Sexual Precocity in Females*

Female patients with this syndrome often exhibit sexual precocity. For example, the catamenia was established before the age of one in a case studied by the authors and the menses were still regular at 54 [Case O R G, M G H 353417, of Albright, Butler, Hampton, and Smith (1937)]

With this sexual precocity there is an associated skeletal and somatic precocity. Thus during childhood these patients grow rapidly and are large for their chronological ages; however, because of early closure of the epiphyses, they usually end by being rather short. No consistent abnormality in gonadal function has been elicited in the male patients.

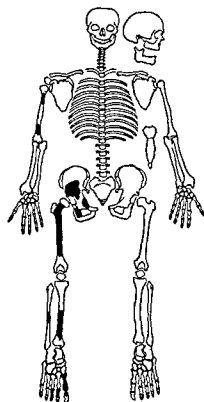


Fig 134 Polyostotic Fibrous Dysplasia. Diagram Showing Distribution of Bone Lesions.

This figure shows distribution of bone lesions on patient M. M. (see Fig. 144). Note typical distribution of lesions in right leg (cf. Fig. 146).

Hyperthyroidism was present in the case of McCune and Bruch (1937) and has been present in repeated subsequent cases (see Case No. 29, p. 276).

II. PATHOLOGIC PHYSIOLOGY

(A) *Nature of Endocrine Disturbance*

In the authors' opinion the onset of puberty is normally the result of the release of gonadotropic hormone or hormones from the anterior pituitary; this release, in turn, is due to stimuli coming over the hypothalamic-pituitary nervous humoral pathway. By 'true precocity' the authors

mean the early release from the pituitary of the gonadotrophic hormone or hormones as the result of some disorder in the releasing mechanism. This is to be differentiated from precocity secondary to a functioning adenoma of some gland which produces gonadal or gonadal like hormones, e.g.



Fig. 13a X-ray Film of Knees of Patient with Polyostotic Fibrous Dysplasia (M.G.H. 35809b) to Show Increased Endosteal Bone Formation as well as Decalcification of Leg Which is the More Involved

[From Albright, Butler, Hampton and Smith (1937)]

granulosa cell tumor of the ovary producing estrin, adrenal cortical tumor producing androgen, *et cetera*

According to this definition precocity in this syndrome is true precocity. Thus case O. R. G. discussed above who had her first catamenia during the first year of life and who was still having periods at the age of 54 was able, in spite of this marked aberration from the normal to have normal twins and one later child in addition. To be sure, at the autopsy at the

age of $6\frac{1}{2}$ years in case 3 of this same series, Dr H Edward MacMahon found no evidence such as recent or old corpora lutea that ovulation had ever occurred, and Sternberg and Joseph (1942) reported similar findings in their case who was autopsied at the age of 13 years, therefore if these two cases are to be considered as examples of true precocity, one must exclude ovulation as a *sine qua non* for true precocity and include any precocity which is mediated through the hypothalamus. It would be interesting to know whether these two children would have started to ovulate at the normal age for puberty.

That the precocity is the result of some lesion in the region of the hypothalamus receives support from the above mentioned autopsy by Dr H Edward MacMahon. This patient who had had her first menstrual period before the age of one was found to have a marked diminution in the size of one mammillary body and an extra nucleus in the adjacent tissue. On the other hand Sternberg and Joseph (1942) failed to find any lesions in the hypothalamus in their case but did find marked hyperplasia of the basophilic cells of the pituitary. This suggests that these cells were being stimulated by some influence possibly a disturbance originating in the hypothalamus.

It is of interest that no case of this syndrome with marked sexual precocity has been described in the male. Furthermore tumors in the region of the pineal body cause precocity only in males—the so-called 'pineal syndrome'. Apparently the mechanism which releases puberty in the male is different from that which releases it in the female. In the first publication from this clinic on this syndrome, an attempt was made to explain this discrepancy between males and females on the ground that whereas the follicle-stimulating hormone (FSH) of the anterior pituitary leads to estrogen formation in the female the luteinizing hormone (LH) of the anterior pituitary leads to androgen formation in the male. It seemed possible that because of some hypothalamic disturbance there is precocious release of FSH but not of LH with resulting production of estrogen in the female but not of androgen in the male.

Two cases were cited in the first publication from this clinic in which individuals afflicted with this syndrome gave birth to twins. FSH is the one hormone which in excess theoretically might lead to multiple ovulations. But the evidence from urinary assays of FSH speaks only for early production not for excess production of this hormone thus cases 1, 2, and 3 of the Massachusetts General Hospital series all three of whom had marked precocity, failed to show an increase of FSH in the urine by a method then being used which is only good for demonstrating too much. More recent studies on a female patient $13\frac{1}{2}$ years old who had her first menstrual period at the age of 6, showed an FSH excretion positive for 13 and negative for 96 mouse units per 24 hours—a normal finding for a normal adult.

(B) *Underlying Nature of the Syndrome*

The triad of features—bone changes, pigmentation, precocity in female—which go to make up this bizarre syndrome is a challenge to those who like to relate one feature of a syndrome to another. The regional distribution of the skin and bone lesions rules out a metabolic or endocrine cause and strongly suggests a neurologic or embryologic explanation. The

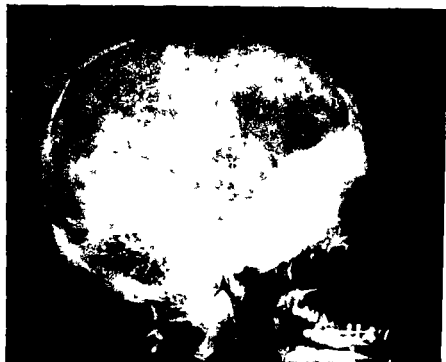


Fig. 136 Case No. 29 Polyostotic Fibrous Dysplasia X-ray Film of Skull to Illustrate Denseness of Bones at Base

precocity, as pointed out above, may well be on a neuro-humeral basis. Thus the one common denominator which might fit all three features of the syndrome is some widespread neurologic disturbance*. This hypo-

* There is an alternative explanation suggested by Thannhauser (1944) which can not be dismissed. He would explain the precocity on the basis of pressure on the hypothalamus secondary to the overgrowth of bone at the base of the skull. It seems just possible that the changes in the mammillary body found at autopsy in case 3 of the M.G.H. series (*vide supra*) might be the result of longstanding pressure on this region. With the exception of case 2 of the M.G.H. series who had marked precocity but no definite thickening at the base of the skull by x ray, it does appear that most of the cases of precocity did have considerable x ray evidence of overgrowth of bone at the base of the skull.

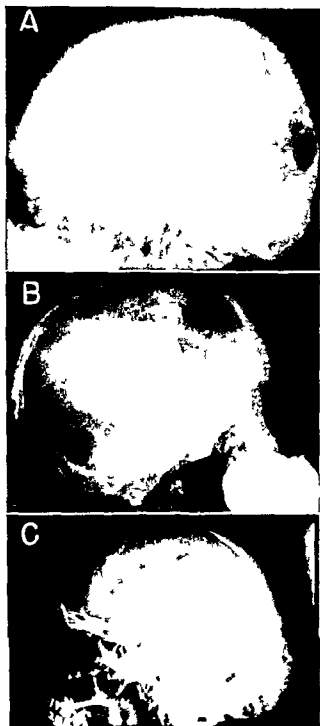


Fig 137 X ray Films of Skulls of Three Patients with Polyostotic Fibrous Dysplasia to Show Denseness and Overgrowth of Bone

Note marked density at base of skull (A) and skull (B) (see also Fig 136), note marked overgrowth of bone in occipital region of skull (C) and to a less extent in skull (A) (see also Fig 145) (A) H W M G II 85619, (B) A C, Children's Hospital 177569, (C) P H, M G II 214900 [From Albright (1947b)]

thesis is supported by the fact that several of the cases with a marked degree of involvement have been mentally deficient. Moreover, Albright, Scoville, and Sulkowitch (1938) found an absent abdominal reflex and

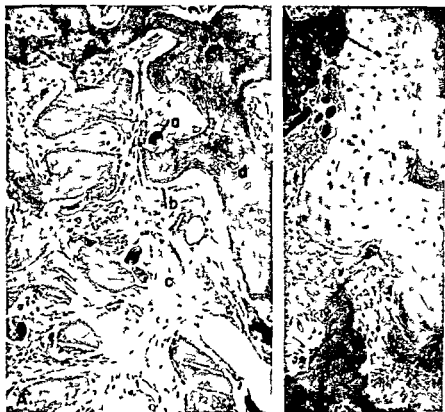


Fig 138 Polyostotic Fibrous Dysplasia Photomicrograph of Bone Biopsy

(A) Note fibrosis (c) many osteoblasts (b) and many osteoclasts (a) note furthermore that trabeculae (d) do not show mosaic structure characteristic of Paget's Disease (see Fig 147A p 288b)

(B) Note island of cartilage (f) Compare with Fig 139 Patient A C Childrens Hospital 17569 [From Albright (1947b)]

an absent cremasteric reflex on the same side as the pigment changes in the skin in one of these cases

(C) *Incomplete Cases of the Syndrome*

The most severe cases usually present all three features. However, it is not unusual to find cases where one or two of the features are missing. Thus *café-au-lait* birth marks are so common they hardly attract attention, and most often occur without the other two features. Bone lesions

in every way typical of this condition can be found without skin lesions and without precocity in females. Kurzrok (1937) reported a case of precocity with areas of pigmentation in whom bone lesions were not recognized though they were not particularly looked for.

III DIFFERENTIAL DIAGNOSIS

There are three conditions to be considered in differential diagnosis hyperparathyroidism with osteitis fibrosa generalisata, lipoid granuloma

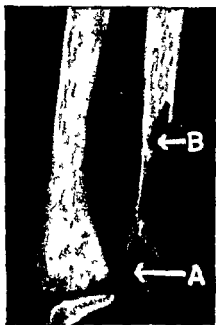


Fig. 139 Polyostotic Fibrous Dysplasia. X-ray Film of the Forearm to Show That Some Bone Lesions May Be the Result of a Dyshondroplasia.

Note marked irregularity of epiphyseal cartilage (A) which strongly suggests that islands of cartilage are being incorporated in the diaphysis. (B) represents such an island. Patient A. C., Children's Hospital 177569. [from All right (1947b)]

matosis (eosinophilic granuloma, Hand-Schüller-Christian's disease, xanthomatosis), and von Recklinghausen's neurofibromatosis.

The features which serve to distinguish the syndrome from hyperparathyroidism have been discussed under that condition (see p. 90).

The following features serve to distinguish the syndrome from lipoid granulomatosis: the bone lesions show only a slight tendency to progress, never clear up spontaneously, and are not radiosensitive; by x-ray one sees increased bone density as well as areas of bone resorption (see Fig. 135 and 136), the bone lesions tend to be segmental in distribution, the serum phosphatase is high in advanced cases, finally, the sexual precocity



Fig. 140 Pigmentation in Neurofibromatosis Contrasted with That in Polyostotic Ectopic Adrenalism.
 Note contrast of areas of pigmentation in (A) as opposed to 'coast of California' contour in (B). Incidentally, note subcutaneous nodules in (B) and their absence in (A). (A) A. K., MGH 26700 with polyostotic fibrous dysplasia. (B) E. D. MGH 363109, with neurofibromatosis. [From All right (1977b)]

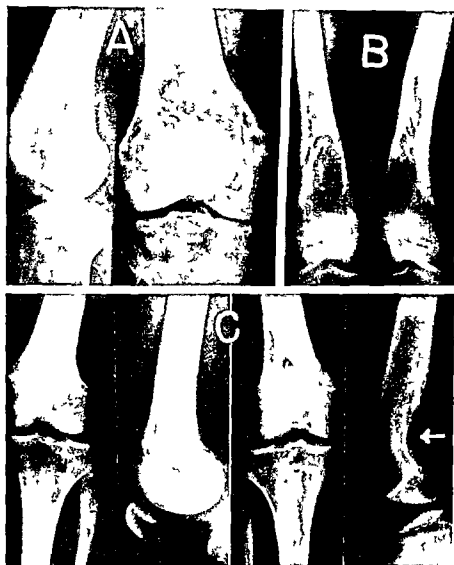


Fig. 141 Bone Lesions in Neurofibromatosis

These illustrate the marked tendency for bone lesions to occur in lower ends of femora and upper ends of tibiae. In (C) note symmetrical lesions in upper ends of both tibiae and similar lesion in lower end of right femur, in lateral view of right femur note that lesion is from without in (A) J H, M G H 401639, (B) C W L, an eleven year old school girl with neurofibromatosis reported by Gorham, Campbell, Howard, Donhauser, and Ruse (1912), (C) F F, M G H 170980 [From Albright (1917b)]

in females and the areas of pigmentation are not features of lipid granulomatosis

The following points differentiate the syndrome from neurofibromatosis: the absence of multiple cutaneous fibromata, the absence of a family history of a similar condition, the sexual precocity in females although sexual precocity in males occasionally occurs in neurofibromatosis as the result of a neurofibroma in the region of the hypothalamus (pineal syndrome), the presence of extensive bone lesions as opposed to a few scattered lesions in neurofibromatosis, the presence of bone lesions which show increased density by x ray, the marked tendency for the bone lesions in neurofibromatosis to be confined to certain areas of predilection especially the lower ends of the femora, the upper ends of the tibiae (see Fig 141), the fact that the areas of cutaneous pigmentation in neurofibromatosis usually have smooth edges like the coast of California rather than wavy edges like the coast of Maine (see Fig 140 and 142), and, finally, the absence of elephantiasis, a common finding in neurofibromatosis.

IV. TYPICAL CASE HISTORY

Case No. 29 Polyostotic Fibrous Dysplasia

The patient N. K., was seen in consultation in January 1945 at the age of 13 years and 10 months. She was referred by Dr. A. H. Kallet of Syracuse, New York. She had previously been thoroughly studied and diagnosed at the Harriet Lane Hospital, Baltimore, by Dr. Lawson Wilkins who kindly made his findings available to us.

Except for areas of cutaneous pigmentation which were noted at birth or within the first four weeks, there was nothing particularly abnormal in the history until the age of six. At that time marked hyperplasia of the nasal mucosa resulted in nasal obstruction and necessitated several local operations by Dr. Carlton W. Bullard of Albany, New York. At about the same time (6½ years) her breasts began to develop and pubic hair began to appear. At 7 years and 1 month she had her first menstrual period. Her menstrual periods were extremely irregular and were not associated with cramps. When seen on January 15, 1945, she had been flowing since the preceding October 4th. The areas of pigmentation had not changed since the first few weeks of life.

In 1942, because of a goiter, tachycardia and a high basal metabolic rate (plus 40), the diagnosis of hyperthyroidism was made; she received Lugol's Solution for 10 days during which her basal metabolic rate fell to plus 20, then Dr. Alfred K. Bates of Albany, New York performed a hemi-thyroidectomy. The pathological diagnosis was colloid goiter. It must be remembered, however, that she had received iodine before operation. The patient improved so much that the other lobe was never removed.

On physical examination (January 1945) her forehead was prominent (see Fig 142) due to increased thickness of the bones at the base of the skull (see Fig 136), a quite characteristic picture presented by patients with this syndrome. Her breasts were moderately well developed (see Fig 142A). She had a moderate growth of pubic hair and some axillary hair. She had characteristic "coast of Maine" areas of brown pigmentation almost confined to the right side of her body (see Fig 142). Her thyroid was easily palpable but there was no bruit; she had no eye signs suggestive of hyperthyroidism. Her heart was forceful; there was

a fine tremor of the hands, the pulse was 112 the blood pressure 145/80 mm of mercury

Roentgenological examination revealed typical lesions of polyostotic fibrous dysplasia confined almost entirely to the right side of the body (see Fig 143) except for the skull where there was bilateral thickening of the bones at the base with obliteration of the frontal and sphenoidal sinuses (see Fig 136) Her right hand was larger than the left the bone age was greater than 16 years and 3 months as judged by the Todd (1937) Atlas of Skeletal Maturation, in fact the crest of the ilium was completely united which makes her bone age at least nineteen This is to be compared with her chronological age of 13 years and 9 months

Laboratory studies basal metabolic rate plus 18 and plus 20 glucose tolerance test normal, serum calcium 8.9 mg per 100 cc serum phosphorus 4.0 mg per 100 cc serum alkaline phosphatase 11.2 Bo lansky units serum total cholesterol 127.0 mg per 100 cc 17 ketosteroid urinary excretion 4.2 mg per 24 hours (low for a post pubertal adult) follicle stimulating hormone (FSH) assay positive for 13 and negative for 96 mouse units per 24 hours (normal values for post pubertal adult)

The menstrual history in this case is very suggestive of non-ovulating ovaries continuously producing estrin which in turn leads to metropathia hemorrhagica This is what one would expect from early production of ISH without luteinizing hormone (LH) Since menstruation which is not associated with a secretory endometrium is likewise not associated with cramps it is of interest that this patient did have cramps for the first time following a five-day course of progesterone This is further evidence of lack of LH stimulation or of an ovarian tissue which is too juvenile to respond to LH The second possibility seems more likely since the 17 ketosteroid excretion was not 0 but 4.2 milligrams, and since we believe that LH stimulates the adrenal cortex to produce 17 ketosteroid precursors [Reifenstein, Forbes, Albright, Donaldson, and Carroll (1945)]

That part of the history which relates to the thyroid gland is quite similar to that of other patients with this syndrome, namely, the presence of a large gland, a moderately high BMR, rapid growth, and more colloid than one would expect at operation

The changes in the mucous membranes of the nose are interesting and should be looked for in other cases They probably represent an effect of estrin

The right sided distribution of bone lesions and of the cutaneous areas of pigmentation is striking (cf Fig 142 A, B, and C, and Fig 143)

PROGNOSIS

Except for case 3 of the Massachusetts General Hospital series, the authors have seen little progression in the extent of the skeletal involvement while under observation That the skeletal disease can be progressive in young children, was well demonstrated in this case 3 and also in the case of McCune and Bruch (1937) Where the skeleton is so extensively involved,



Fig. 142 Case No. 20 Polycystic Fibrous Dysplasia Photograph showing Pigmented Areas
Note right side distribution (cf Fig. 143)

secondary lesions may arise which are incompatible with prolonged life, thus, the chest may be so deformed that a cor pulmonale is inevitable. Pathological fractures are common and usually heal well with exception of those of the upper ends of the femora (*vide infra*). The endocrine disorder may be most benign, case 2 of the MGH series had her first menstrual period at the age of one and passed through an artificial menopause at the age of 51.

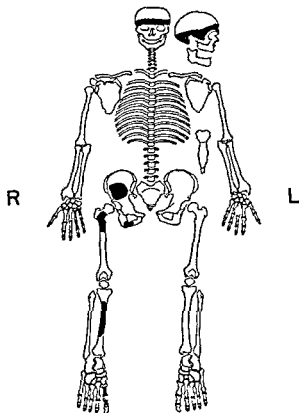


Fig 143 Case No 29 Polyostotic Fibrous Dysplasia Diagram Showing Distribution of Bone Lesions

Note right-sided distribution except in skull (cf Fig 142)

VI TREATMENT

There is no known treatment other than orthopedic therapy for the skeletal deformities and fractures as they occur. One of the most disabling features of this syndrome is bowing of the upper ends of the femora which leads to repeated fractures. Many of these do not completely unite and result in pseudarthroses. Orthopedic measures which do not restore



Fig 111 Successful Operative Repair of Stereoid Croak Deformity of Hip of Patient with Pyloric Dysplasia
 (A) x-ray film on 11/4/31 before operation (B) x-ray film on 2/12/43 shortly after operation



Fig. 144 (continued)

(C) x ray film on 8-3-43 showing excellent end result, (D) diagram to explain nature of operation. Published with permission of Dr. H. P. Lange, the surgeon.

weight-bearing lines are useless because of the lack of rigidity of the bone. The best result in the management of this serious complication which has come to the authors' attention is that of a patient operated upon by Dr H P Lange. The nature of the operation and the result are both shown in Fig 144 A, B, C, and D.



Fig 145 Illustration from von Recklinghausen (1891) Usually Considered to Be an Example of Osteitis Fibrosa Generalisata von Recklinghausen

Because of the marked "shepherd crook" deformities of the upper halves of the femora (compare Fig 144A) and because of the bulge in the occiput (compare Fig 137A and 137C) the authors feel quite certain that this is an example of polyostotic fibrous dysplasia.

VII TERMINOLOGY

In regard to the name to be used for this bizarre condition, the authors quote from the section entitled 'Wanted A Name', from a previous article [Albright (1947b)]

"Since the etiology of the syndrome remains quite obscure, the author and his colleagues, Drs Allan M Butler, Aubrey O Hampton, and Patricia Smith, with the following exception (1937) and the descriptive designation

'Osteitis Fibrosa Disseminata with Areas of Cutaneous Pigmentation and an Endocrine Dysfunction with Precocious Puberty in Females.' Because of the unwieldiness of this terminology and because A precedes B, H, and S in the alphabet and probably for no other reason the term, Albright's Syndrome, came into being "

'The use of a person's name for the designation of a syndrome has objections, the chief one being that no one can decide whose name to use. One can always go to the literature and find some preceding reference to a case which in all likelihood had the syndrome in question. Often each language produces its own 'first' describer. In this connection the present author, a number of years ago, ran into a rather amusing state of affairs. The question as to the terminology of this syndrome had come up and he thought it would be of interest to look over von Recklinghausen's original 1891 monograph, which includes the description of a number of different bone conditions, to see whether by any chance a case with this syndrome had been described. It turned out that one and probably two of the three famous cases in the monograph (*cases 5, 6 and 7*) which had been considered as examples of osteitis fibrosa generalisata and hence of hyperparathyroidism, most surely had not been afflicted with hyperparathyroidism but with this syndrome (see Fig 145). Fortunately, as the present author pointed out at the time [see discussion of paper by Kornblum (1941)] von Recklinghausen's third case (*case 7*) in all probability did have hyperparathyroidism, otherwise we would be confronted with the disturbing state of affairs that von Recklinghausen had neglected to describe what is now known as von Recklinghausen's disease of bone. It will be seen, therefore, that as far as the bone manifestations of the syndrome are concerned von Recklinghausen preceded the author and his colleagues by 46 years. Thus, there is as much reason to connect von Recklinghausen's name with this bone disease as with osteitis fibrosa generalisata."

There is probably one simple way out of the above dilemma. After all, the most striking feature of the syndrome is perhaps the bone disease. A descriptive name for the bone disease could be found and the whole disease could go under this name. This is exactly what is taking place. The tendency is to use the name, polyostotic fibrous dysplasia*, suggested by Lichtenstein (1938), rather than the name, 'osteitis fibrosa disseminata', suggested by the author and his colleagues. The present author has no fault to find with this tendency. A case with precocity and cutaneous pigmentation but without evidence of bone lesions such as that described by Kurzrok (1937) could be designated 'polyostotic fibrous dysplasia *sine fibrous dysplasia*' "

* Lichtenstein and Jaffe (1942) [see also Jaffe and Lichtenstein (1942)] subsequently omitted 'polyostotic' in order to include those cases where the condition is confined to one bony lesion and simply called the disease 'fibrous dysplasia'.

CHAPTER 9

PAGET'S DISEASE (OSTEITIS DEFORMANS)

I MORBID ANATOMY

If one defines a 'localized bone-disease' as one that is not generalized, Paget's disease [Paget (1877)] is localized. It may be limited to one bone or be widely spread throughout many bones, but it is not generalized (see Fig 38, p 80). One can almost invariably find somewhere a sharp line of demarcation between normal bone on one side and Paget's disease on the other. The very fact that Paget's disease is not generalized is strong evidence against its being a metabolic or endocrinologic disorder. The reader may well ask, "What about the bone cysts in hyperparathyroidism?" But these are secondary complications, the underlying lesion decalcification, is generalized. The reader may then ask "What about post menopausal osteoporosis, in which the bone lesions tend to be confined to the spine and pelvis?" There the disease is following a well-defined pattern certain parts of the skeleton are more prone to involvement than others and the distribution of the lesions is not spotty but according to plan, it is not as though the twelfth thoracic and third lumbar vertebrae were involved whereas the remaining vertebrae were normal.

Having made the above rather dogmatic statement, we must make one reservation. We have in our clinic a patient with undoubted Paget's disease in whom every bone in the body is involved, moreover, each bone is at the same stage of the disease. Unfortunately, the patient refuses to be hospitalized for detailed studies.

Paget's disease, we attest then, has a spotty distribution. This is consistent with an infection, a tumor, a trophic nerve disturbance, or a vascular lesion. There is a lot to suggest that the fundamental disorder is vascular. The condition increases with age, there is a tendency to arteriosclerosis in general and to arteriosclerosis of those arteries supplying the involved bone in particular, there is a tendency for the condition to run in families [Koller (1946)]. However, if the disease is on a vascular basis, it must be due to an abnormality that leads to too much circulation rather than too little. Thus, the skin overlying an involved bone shows an increase in temperature, when Paget's involves the skull there is a marked increase in the size and tortuosity of the superficial arteries of the temporal region. As a cause for too much blood flow one considers a shunt between the arterial and venous systems, i.e., what amounts to an arteriovenous aneurysm. Support for this concept was provided recently by Edholm, Howarth and McMichael (1945) who found that the blood flow through bones involved with Paget's disease is increased up to 20 times the normal. Moreover,

when the condition is sufficiently widespread there is a decrease in arterio-venous oxygen difference, an increased total blood flow, and heart failure.

Paget's disease has a predisposition for that part of the skeleton which is most subject to stresses and strains. Thus the sacrum is the bone most often involved, the lumbar vertebrae are more often involved than the thoracic and the thoracic more often than the cervical, the lower extremities more often than the upper. One may ask why the skull is so often involved. The answer is not apparent, but even here stresses and strains play a part as shown in Fig. 146 where the distribution of the involved area of the skull is apparently determined by the pull of the temporal muscles.

When one comes to the actual bone lesion in Paget's disease it has much in common with that seen in osteitis fibrosa generalisata (compare Fig. 147A and 147B). In both conditions the bone lesions are extremely vascular, there is marked fibrosis, about half the bone surface is covered with osteoclasts as evidence of marked bone resorption and about half with osteoblasts as evidence of marked bone repair, and the bone that is being laid down is being calcified, as shown by the normal width of the osteoid seams. There are however some differences. There is not the same tendency to the formation of so-called osteoclastomas or brown tumors in Paget's disease as in osteitis fibrosa generalisata. The most important distinction between the two conditions, however, concerns the architecture of the bone. In Paget's disease, for reasons that will appear below, the trabeculae start nowhere and end nowhere, in osteitis fibrosa generalisata there may be extreme decalcification, but those trabeculae that are left are in good mechanical arrangement. A third difference between the two conditions has to do with the so-called mosaic structure, as first described by Schmorl (1932). This pathognomonic feature of Paget's disease is due to the bizarre arrangement of the cement lines within the trabeculae (see arrows in Fig. 147B). To be sure, there are other bone diseases with an increased number of cement lines in the trabeculae, but the lines are not so completely irregular. The reason for this will be discussed below.

From the above discussion it is evident that in Paget's disease there is a marked increase in both bone destruction and bone formation; in other words, there is an increased turn over of bone. If one had to guess, one would presumably say that the increased bone formation was the result of increased bone destruction. But one does not have to guess, one can examine the initial lesion. To discover what is going on in a complicated pathologic picture, one should always try to get at the advancing edge of the lesion and see what comes first.

In the skull in Paget's disease one often finds lesions that have quite a different appearance from those encountered in other parts of the skeleton. They lack the marked overgrowth of bone and consist merely of circum-

scribed areas of bone destruction. The x ray appearance of such a lesion is shown in Fig 148A. The involved area terminates abruptly (see arrows). At autopsy a section through such an area (Fig 148D) showed normal bone (to the right of the arrow) sharply demarcated from the involved bone (to the left of the arrow). A microscopic examination at this point (Fig 148E) revealed normal bone (to the right) being destroyed by the destructive lesion (to the left) with numerous osteoclasts; no bone formation or osteoblasts were seen. This is strong evidence that the initial lesion in Paget's disease is bone destruction.

Support for this contention can be derived from the characteristic manner in which the disease progresses. Thus x ray films of an involved skull (Fig 149A) show three zones: normal bone (to the right), bone destruction and bone repair with overgrowth and increased density (to the left). If such an area of involvement is followed for several years the zone of bone destruction in some cases may be seen to advance. Such was the case in this skull in which the lesion advanced into the normal bone closer to the nose (Fig 149B). In the long bones for reasons that will appear below the bone repair usually occurs almost simultaneously with the bone destruction and one seldom has the opportunity to see one process divorced from the other; occasionally where one does (Fig 149C, D and E) the same sequence of zones appears. Schmorl (1932) also demonstrated that the initial lesion in the long bones is bone resorption. He did this by making a longitudinal section of an involved long bone from which he took a cross section 2 cm. distal to the point where the bone was involved grossly enough to be detectable by the naked eye. This cross section showed bone destruction without any evidence of bone formation.

II. LABORATORY FINDINGS

The serum calcium and phosphorus are usually normal in Paget's disease although there is a slight tendency for the serum phosphorus to be

Fig 146 Acute Paget's Disease of Skull with a Distribution Suggesting that Pull of Temporal Muscles Is a Factor

(A) Lateral x ray of skull. Note that bone on posterior aspect of skull is of normal texture and that bone in front of skull has been largely destroyed. Note especially two semicircles, one in each side of skull which represent border between normal bone and Paget's disease.

(B) Antero-posterior x ray of skull. Note that two semicircles meet in the front, albeit not quite in the middle.

(C) Anatomical drawing from Gray's Anatomy. Note that pull of temporal muscles may well account for peculiar distribution of acute Paget's of the skull shown in A and B.

Finally note that at the lowermost part of the occipital bone is also involved in acute Paget's disease presumably due to the pull of the muscles of the back which are attached to this area.

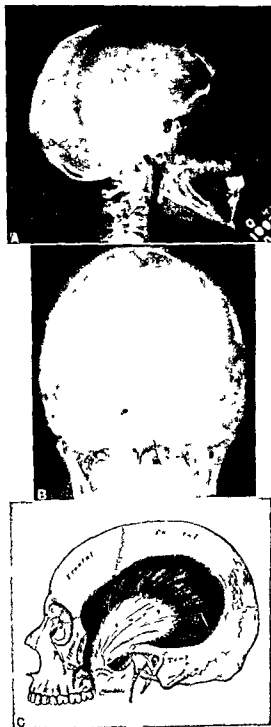


FIG 146

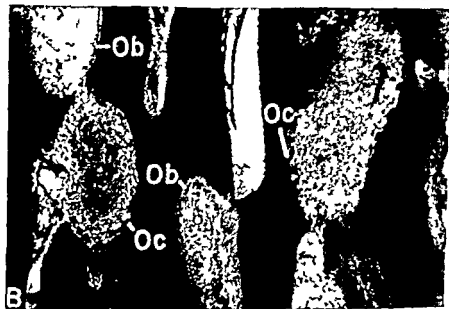
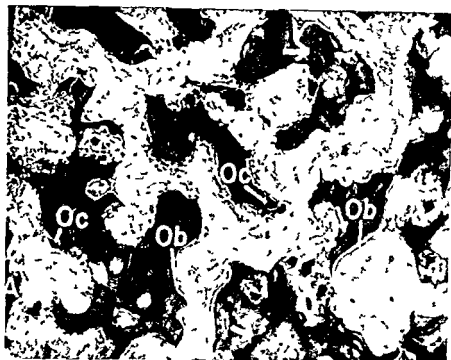


Fig 147 Photomicrographs of the Bone in Paget's Disease (A) and Hyperparathyroidism (B)

Note that although the osteoclasts (Oc) and the osteoblasts (Ob) are present in both diseases the structural integrity has disappeared in A but is maintained in B. Note also the mosaic appearance of the cement lines some of which are indicated by arrows. [From Reifenstein and Albright (1944) these photographs were kindly supplied by Dr Granville A Bennett to whom the authors are greatly indebted.]

slightly elevated, the serum phosphatase level is higher per unit of bone disease in Paget's disease than in any other condition. Since the serum phosphatase is an index of bone formation (see p. 6) this agrees with the marked overgrowth of bone which one finds in Paget's disease and with the tendency to unbridled bone formation—that is, to osteogenic sarcoma. When the disease is progressing calcium and phosphorus excretions in the urine may be increased and urinary calculi are not infrequent findings.

III. X-RAY DIAGNOSIS

The x-ray diagnosis should offer little difficulty. One looks at the advancing edge of a Paget's lesion for the following three zones: normal bone, zone of bone destruction, and zone of overgrowth of bone. Furthermore, one looks for increase in the size of the bone, for the characteristic large coarse trabeculations, and for bowing of the long bones. The classical finding in the skull, of course, is a thick, 'coarsely moth-eaten' skull (Fig. 27E, p. 61) as opposed to the normally thick, 'finely moth-eaten' skull of osteitis fibrosa generalisata (Fig. 27B and C, p. 60).

IV. RELATION OF PAGET'S DISEASE TO PARATHYROID FUNCTION

Whereas it has been established beyond all doubt that Paget's disease is not a manifestation of hyperparathyroidism, there have been several cases where hyperparathyroidism was complicated by Paget's disease. The authors have seen four such cases. Since Paget's disease is a very common disease (three per cent of everybody over 40 has Paget's disease according to Schmorl¹) it is not unlikely that the occurrence of the two conditions in any one individual is pure coincidence. On the other hand, it is just possible that the presence of hyperparathyroidism predisposes patients to develop Paget's disease and it is the authors' practice to rule out hyperparathyroidism in all cases of Paget's disease. This practice to date, however, has not uncovered any cases of hyperparathyroidism.

Furthermore, it seemed possible that a surgically induced hypoparathyroidism might benefit Paget's disease. Since hypoparathyroidism is now easily controlled (see p. 35) we felt justified in removing all four parathyroids from a desperate case of Paget's disease. This was carried out by Dr. Oliver Cope and hypoparathyroidism was induced. Whereas there may have been slight improvement, it was not dramatic.

V. PATHOLOGIC PHYSIOLOGY

The pathologic lesions of Paget's disease have been discussed; it remains to attempt an interpretation. It is clear that the initial lesion is a localized factor causing bone destruction, which has no respect for structural requirements. The bone destruction renders the involved bone more susceptible

to stresses and strains. To compensate for this, the osteoblasts are stimulated to lay down more matrix, the serum phosphatase level—an index of osteoblastic activity—therefore rises. Where the stresses and strains are constantly present, as in the vertebrae and long bones, bone repair occurs almost simultaneously with bone destruction, where stresses and strains are minimal, as in the skull, bone repair may lag behind bone destruction (*vide supra*).

In the meantime, the localized destructive factor persists and continues to destroy bone, including some that has been newly laid down as a reparative process. The junctions between new and old bone are marked by cement lines, in the constant battle between bone destruction and bone repair many such lines arise. Since the local destructive factor has no respect for the mechanical requirements of the skeleton the lines have no order, hence the morbid structure (see arrows in Fig. 147B). There results a bone of poor architectural value. This factor explains three of the striking clinical characteristics of the disease: the marked tendency to overgrowth of bone, the fact that the serum phosphatase level—an index of bone repair—is so high per unit of diseased bone, and the tendency of the bones to become deformed in spite of marked overgrowth—for example bowed femurs.

In Fig. 150A the sequence of events is illustrated schematically.

VI. EFFECT OF IMMOBILIZATION ON PAGET'S DISEASE

(A) Loss of Stress and Strain

When a bone containing Paget's disease is immobilized the stimulus for bone formation ceases, and bone destruction continues unabated. There results a decrease in the serum phosphatase level and in bone mass and an increase in the urinary excretion of calcium (Fig. 150B). There may even be hypercalcaemia when the amount of calcium to be excreted exceeds the ability of the kidney to excrete it (Fig. 151) or when the kidney function becomes impaired from hypercalcaemia.

The role of immobilization in producing osteoporosis and the acute atrophy of disuse that results when a patient in whom the turnover of bone

Fig. 148 Photographs Showing that the Initial Lesion in Paget's Disease Is Bone Destruction

A—the x ray film of a skull with two areas of destruction separated by a bridge of normal bone (between the arrows). B—the x ray film of the same skull post mortem. C—the skull as it appeared post mortem. D—a section through this skull showing the advancing edge of destruction (arrow) with normal bone to the right and involved bone to the left. E—a photomicrograph of the area at the point of the arrow in D showing normal bone on the right and the initial lesion of bone destruction on the left with osteoclasts (arrow) in juxtaposition to the normal bone. [From Reifenstein and Albright (1944).]

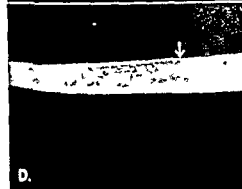




Fig 143 The Progression of Paget's Disease

A—skull showing an area of destruction with normal bone to the right and left, crown 1 one to the left B—the same skull 3 years later showing it at the area of destruction has moved closer to the nose

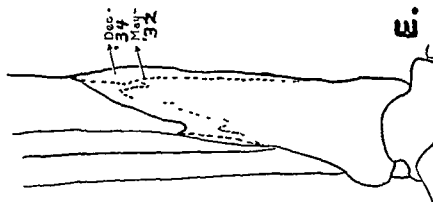


Fig 149 (continued)

C—involverment of the tibia D—same tibia two and a half years later E—diagram indicating the progression of the lesion in the tibia. [From Reifenstein and Albright (1944)]

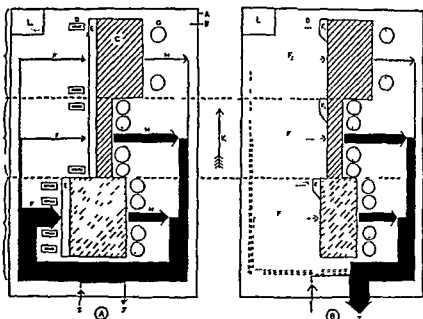


Fig 150 Schematic Diagrams Showing the Processes in Uncomplicated Paget's Disease (A) and in Paget's Disease after Immobilization (B)

Three stages or zones are depicted I, normal bone II bone destruction III bone destruction with compensatory repair

Uncomplicated Paget's Disease The designations are as follows A—body limits B—body fluid, C—bone mass having three surfaces (one where nothing is happening one where bone is being resorbed and one where it is being laid down) D—osteoblast laying down a matrix of osteoid tissue (E) F—arrow indicating by its size the rate of deposition of calcium and phosphorus G—osteoclast H—arrow indicating by its size the rate of resorption of calcium and phosphorus I—calcium and phosphorus entering the body through the gastrointestinal tract J—calcium and phosphorus leaving the body by the kidneys and other exits K—arrow indicating the direction of advancement of the disease process In Zone II, note the decrease of the bone mass the increase of osteoclasts and the increase in the rate of resorption of calcium and phosphorus In Zone III note that the increased stresses and strains from the decreased bone mass in Zone II have resulted in an increase of osteoblasts an increase in the rate of deposition of calcium and phosphorus and an increase in bone mass which is of poor quality Analyses of the serum (L) show a normal calcium level a slightly elevated phosphorus level and a markedly elevated phosphatase level

Paget's Disease after Immobilization The osteoblasts (D_1) are hypoplastic owing to loss of the stimulus of stresses and strains through immobilization this results in a decrease of matrix (E_1) and a decrease in the deposition of calcium and phosphorus (F_1) In Zone III note that the huge amount of compensatory bone formation (F) is no longer present because of immobilization Since bone destruction (II) continues unabated there results not only a marked diminution of the bone mass (C) but also a tremendous increase in the excretion of calcium and phosphorus in the urine (J_1) Analyses of the serum (L_1) show a markedly elevated calcium level a slightly elevated phosphorus level and a phosphatase level that is still slightly elevated

[From Reifenstein and Albright (1944)]

is greater than in the normal adult is immobilized are discussed elsewhere (see *Osteoporosis from Disuse*, p 147)

Case No 30 illustrates well the sequelae of immobilization in a patient with Paget's disease. The serum phosphatase fell from 42 to a low of 13 Bodansky units, the serum calcium gradually climbed from 10.1 to a high of 13.9 mg per 100 cc, this high point coinciding with the low point on the phosphatase curve, the daily calcium excretion in the urine reached 519 mg. When activity was resumed the values returned to the pre fracture levels, the daily calcium excretion in the urine falling to 38 mg.

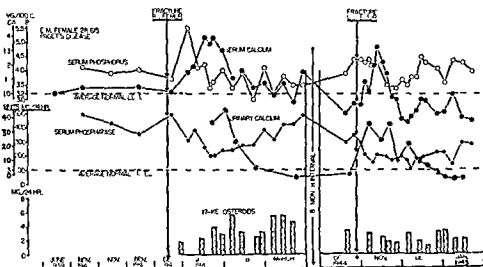


Fig 151 Case No 30, Paget's Disease Chart Illustrating the Effect of Fractures on the Serum Calcium Phosphorus and Phosphatase Levels and on the Urinary Excretion of Calcium and 17 Ketosteroids
[From Reifenstein and Albright (1944)]

Case No 30 Paget's Disease, Fracture of Right Femur, Osteotomy of Left Femur, Post Menopausal Osteoporosis, Acute Atrophy of Disuse

L M (M G H 281615), a 61 year old woman, was admitted to the hospital on December 28 1912, with a fractured femur

At the age of 50 she had become aware of enlargement of the head and the left clavicle. A ray examination had revealed Paget's disease. At the age of 57 she had noticed bowing of the femurs. For some years she had been troubled with increasing deafness and ringing in the ears. She had never passed gravel. A physiologic menopause without hot flashes had occurred at the age of 52. In June, 1939, she had been referred to one of us (F A) by Dr Louis Hamman of Baltimore.

The x ray films of the femurs obtained in 1939 (Fig 152A) explain why it is possible in Paget's disease for a bowed leg to be as long as if not longer than the unbowed leg. This question had been raised and answered by Schmorl. It will

be seen that a series of partial fractures had occurred on the convex side. Each such fracture leads to an increase in length of a fraction of a centimeter. A series of such fractures can increase the length by several centimeters. These partial fractures are of clinical importance since a complete fracture may occur at one of these points. Such was the case in the patient under discussion (see Fig. 153), the site at which the fracture subsequently developed is indicated by the arrow in Fig. 152A.

Physical examination in June 1939 revealed the typical picture of Paget's disease with great enlargement of the head, marked overgrowth of the jaws and enlargement of the left clavicle and both femurs. The blood pressure was 135/90. There were present a basal systolic murmur and a thrill that were interpreted as aortic stenosis on an arteriosclerotic basis. The serum calcium level was 10 mg per 100 cc. The urine contained a moderate amount of calcium and the sediment showed 10 to 15 white cells per high power field.

The patient was advised to take one glass of milk and 10 drops of viosterol three times a day. She was seen at about yearly intervals thereafter. The blood chemistry findings at these visits are given in Fig. 151. In November 1941 a urine examination showed a specific gravity of 1.030, no albumin, a moderate amount of calcium and 20 to 30 red cells and 4 to 6 white cells per high power field. At that time the milk intake was reduced to two glasses a day and the viosterol intake was decreased to 10 drops twice a day. In addition sodium citrate 2 gm three times a day, was prescribed.

On November 19, 1942, the urine showed a specific gravity of 1.002, no albumin and 2 red cells and 4 white cells per high power field. The serum calcium was 10.4 mg per 100 cc, the serum phosphorus 4.0 mg and the serum phosphatase 28.0 Bodansky units.

On December 28 the patient slipped on the floor and fractured her right femur at the junction of the middle and distal thirds. She was admitted to the Baker Memorial Hospital under the care of Dr. George W. Van Gorder*. A ray examination showed the fracture fragments to be in satisfactory alignment; hence no orthopedic procedures were instituted except simple traction (Fig. 152B).

The course thereafter is shown in Fig. 151. Because of previous experience in another case, milk was omitted from the diet from the time of admission and other fluids by mouth were forced so far as possible. The patient remained comfortable for the first three weeks. Then as the serum calcium began to rise she complained of anorexia and dryness in the nose and throat with difficulty in swallowing. This was followed by constant nausea and vomiting. The fluid intake became inadequate. For the next three weeks, during the period of maximal hypercalcemia, the patient was given almost daily an intravenous infusion of 1000 to 2000 cc. of equal parts of 5 per cent dextrose and normal saline solutions. On February 8, 1943, when the serum calcium level had fallen to 11.6 mg per

* We are indebted to Dr. Van Gorder for his co-operation in the study of this patient.

Fig. 152 Case No. 30, Paget's Disease. X-ray Films Showing the Right Femur Three Years Before (A) and Immediately (B) Three Weeks (C), Five Weeks (D) and Ten Weeks (E) After Fracture.

The point of fracture is indicated by the arrow. Compare the densities of the cortices in these films. [From Reifenshtein and Albright (1944)]



FIG 152

100 cc, the intravenous infusions were discontinued. At the same time the gastric and pharyngeal symptoms practically disappeared and thereafter the patient was able to maintain an adequate fluid intake by mouth.

X-ray films taken on January 18, 1943 (Fig. 152C) 21 days after the fracture showed that the alignment had been maintained and that a marked amount of



Fig. 153 Paget's Disease Showing Fracture through the Site of a Previous Infracture

Other infractures above and below the fracture are indicated by arrows. [From Reifenstein and Albright (1944)]

calcified callus was already present. The bone healed so rapidly that by the first week in February the traction could be removed and by February 15 the patient was able to get out of bed. The subsequent course was uneventful. This case was mentioned in a previous communication [Reifenstein and Albright (1944)].

As the result of the fracture of the right femur the patient had legs of unequal length, and she had considerable difficulty in walking. She elected therefore, to have Dr. Van Gorder perform an osteotomy on the left femur in order to straighten that leg. This was carried out on October 27, 1944. Because of our

previous experience with her, she was watched carefully. The same sequence of events occurred as after the original fracture (see Fig 151). The patient complained of anorexia, dryness of the nose and throat, difficulty in swallowing about 10 days after operation at a time when her urinary calcium excretion had risen from a normal level to 423 mg per 24 hours and her serum calcium level had begun to rise. It was necessary to give daily for 27 days an intravenous infusion of dextrose and saline solutions to support the patient because of constant nausea. The infusions were finally discontinued on December 3, 1944. Thereafter the patient made rapid progress and was discharged on February 3, 1945 able to walk unassisted. At the time of discharge the serum calcium was 8.1 mg per 100 cc, the serum phosphorus 4.0 mg per 100 cc, the serum alkaline phosphatase 21.2 Bo lansky units, the serum protein 5.7 gm per 100 cc, and the urinary calcium 36 mg per 24 hours.

Two months later she reported that her gait had been much improved by the corrective operation. The serum calcium was 7.6 mg per 100 cc, the serum phosphorus 4.2 mg per 100 cc, and the serum alkaline phosphatase 31.4 Bo lansky units.

(B) Possible Role of the Alarm Reaction

The decreased formation of bone in Case No. 30 was probably not entirely due to immobilization. As with any injury [Forbes, Donaldson, Reifensstein, and Albright (1947)] there was a depression of the urinary 17-ketosteroid excretion, with a return to a normal value for a patient of this age with recovery—from 1.7 mg in twenty-four hours on the third day after injury to 5.5 mg on the seventy-seventh day. It is quite probable that this change in the 17-ketosteroid excretion and part of the depression in bone formation are to be attributed to an alteration of adrenocortical function that is common to all injuries [compare the so-called Alarm Reaction of Selye (1946), see p. 182]. The net result of this altered function following injury is a curtailment of tissue formation except at the site of injury [Albright (1942-1943)]. Ordinarily such a curtailment may be overlooked but in Paget's disease, where bone formation is rapid and extensive, any influence that suppresses it is magnified.

It should be noted that this curtailment of tissue anabolism following injuries does not affect the anabolism at the site of the injury. It is not unlikely that there is some local factor that causes maximal tissue repair there. Thus in Case No. 30 while the rest of the femur was melting away, a good callus was being put down at the site of the injury.

(C) Dangers and Their Prevention

When a patient with Paget's disease is immobilized the danger of a so-called "chemical death" exists (see p. 77). Thus, the patient in Case No. 30, if treated in the ordinary fashion with liberal amounts of milk, no special regard for fluid intake, and more than minimal immobilization, might well have developed an even higher blood calcium level, anuria, and



death. Metastatic calcification in the lungs might have been overlooked at autopsy and the cause of death put down as bronchopneumonia. To control the hypercalcemia and hypercalcuria one should prescribe a low calcium diet and sufficient fluid by vein if need be so that the serum and urinary calcium concentrations do not rise to dangerous levels. Immobilization should be kept at the absolute minimum and mobilization should be begun as early as possible not only to avoid chemical death but to avoid extreme atrophy of the bones (Fig. 154).

Besides nausea and vomiting which are recognized symptoms of hypercalcemia, both this patient and another individual previously studied experienced a peculiar sensation of dryness in the nose and throat, with difficulty in swallowing. These symptoms seemed to be associated with the hypercalcemia.

VII. TREATMENT

Since the initial lesion is increased bone resorption it seems logical to administer those agents which decrease bone resorption, namely high calcium and phosphorus intakes, vitamin D to increase calcium absorption and perhaps an alkalinizing salt. Specifically, most of the authors' patients receive at least two glasses of milk or buttermilk daily, and 50,000 units of vitamin D concentrate three times weekly. Alkalinizing salts are seldom used because of the danger of causing kidney stones while on a high calcium and phosphorus regimen. In female patients after the menopause estrogen therapy is probably indicated to enhance compensatory bone repair (see Metabolic Study No. 5, Case No. 12 p. 154). Vitamin C in large doses, for reasons which are not apparent, seems to benefit some cases. The results of therapy, unfortunately, are impossible to evaluate.

For reasons which have been discussed above, low calcium, phosphorus and vitamin D intakes and a high water intake are prescribed for patients with Paget's disease who are immobilized with fractures or confined in bed for any reason. Since estrogen therapy decreases the calcium excretion following orthopedic operations (see p. 147), it might also be tried under these circumstances. In male patients where the production of sterility would be a factor of importance, estrin therapy is probably contra-indicated.

very little calcium in the urine (see p 36), and lowers the dose if the converse is true. He thus avoids hypocalcemia with its penalty of tetany and hyperhyperparathyroidism with its threat of death (see p 77).

(3) In a patient with kidney stones or rarified bones where one wishes to rule out hyperparathyroidism and where the serum calcium and phosphorus values are equivocal, a persistently positive Sulkowitch test at the 3 to 4 plus level will favor hyperparathyroidism and call for further deter-

TABLE 8

*Factors Used in Deriving Certain Components of Muscle Protoplasm From Nitrogen (N)**

Factor Number	Component to Be Derived	Final Unit	Factor**
1	Protein in Protoplasm	gm	6.25
2	Protoplasm fat free but not extracellular fluid free	gm	32
3	Protoplasm fat free and extracellular fluid free (true muscle) [Talbot, Butler and MacLachlan (1913)]	gm	27
4	Intracellular Fluid in Protoplasm	cc	19
5	Extracellular Fluid in Protoplasm	cc	5
6	Potassium in Intracellular Fluid of Protoplasm	meq	2.7
7	Sodium in Extracellular Fluid of Protoplasm	meq	0.77
8	Phosphorus in Protoplasm	gm	1/14.7 (=0.068)
9	Sulfur in Protoplasm	gm	1/14.5 (=0.069)
10	Fat Calorically Equivalent to Protoplasm	gm	2.8
11	Protoplasm (fat free) Minus Fat Calorically Equivalent to Protoplasm	gm	29.2

* For source of factors see Rosenfeld, Albright and Wells (1915)

** Factor \times nitrogen in grams = component

minations of the serum chemistries whereas a test that is positive only at the 1 plus level will practically rule it out (see p 73).

II. THEORETICAL PHOSPHORUS BALANCE

By a theoretical phosphorus balance is meant that balance which one would expect from the nitrogen and calcium balances. Since about 97 per cent [Shohl (1939a)] of the body phosphorus is contained either in bone (calcium to phosphorus ratio = 2.23) or as an integral part of protoplasm (nitrogen to phosphorus ratio of muscle = approximately 11.7), it is possible if one knows the calcium and nitrogen balances to calculate how much of the

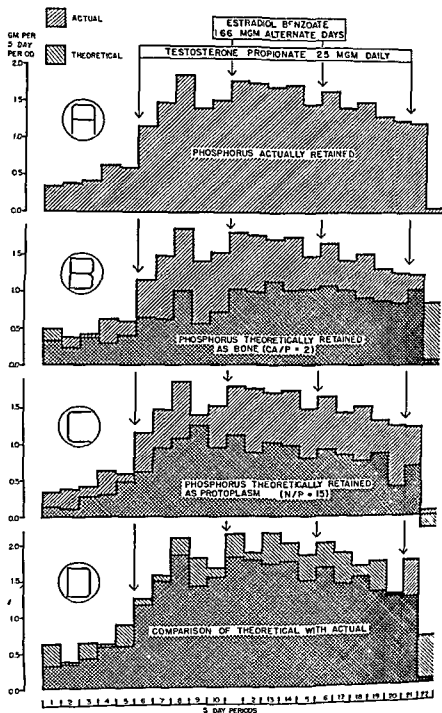


Fig 155

phosphorus balance can be explained by the balances of these two. For the purpose of these calculations all protoplasm can be considered to have the same composition as muscle, since most of the protoplasm is muscle, and since the N/P ratio in other tissues is not very different from that in muscle [skin, 16.6/1, muscle, 17.2/1, liver*, 10.3/1, spleen, 11.1/1, kidney, 12.8/1, and brain†, 6.6/1—Albright (1942-1943)] Similarly, it is possible to calculate a theoretical nitrogen balance if one knows the phosphorus and calcium balances or a theoretical calcium balance if one knows the nitrogen and phosphorus balances. In Table 8 are given the factors involved in the calculation of certain components of muscle protoplasm from nitrogen.

In Fig. 155 an analysis is made of the phosphorus, calcium, and nitrogen balances during a metabolic experiment in which marked fluctuations of the balances were induced by starting and stopping testosterone propionate therapy (see Case No. 13, Metabolic Study No. 6, page 162). This figure illustrates that the phosphorus balance very nearly can be accounted for by the calcium and nitrogen balances during both the control observations and the experimental periods. During the 22 five-day periods 29.1 gm. of

* The ratio of liver is affected by phosphorus present in glycogen.

† The ratio of brain is affected by phosphorus present in phospholipids.

Fig. 155 An Analysis of the Calcium, Phosphorus, and Nitrogen Balances in a Metabolic Experiment

This study on an elderly male patient with osteoporosis (M. H., M. G. H. 267511) consists of 22 five-day periods. (See Fig. 78, page 163 and Case No. 13, Metabolic Study No. 6, page 163). The ordinates are the scales for balances in grams per five-day period, the abscissa is the scale for five-day periods. The horizontal line starting at zero of the ordinate is the baseline; balances extending from the baseline toward the top of the chart are positive, those extending from the baseline toward the bottom of the chart are negative.

The chart has four divisions: (A) the measured phosphorus balance, (B) the measured phosphorus balance with superimposed theoretical balance explainable by the measured calcium balance ($\text{Ca/P} = 2$), (C) the measured phosphorus balance with superimposed theoretical phosphorus balance explainable by the measured nitrogen balance ($\text{N/P} = 15$), and (D) the measured phosphorus balance with superimposed theoretical phosphorus balance explainable by both the measured calcium and the measured nitrogen balances, i.e. a summation of B and C. It will be noted in D that the actual phosphorus retention very closely follows the theoretical phosphorus retention. As a matter of fact, if a ratio of Ca/P of 2.23 instead of 2 had been used in constructing the chart, the discrepancy would be very much less. This experiment supports the contention that nearly all of the phosphorus retained as a result of testosterone propionate therapy is retained either as bone or as protoplasm.

For further discussion see text. Additional data on this patient are published elsewhere (Reifenstein, Albright, Parson, and Bloomberg (1942), Albright (1942-1943), Reifenstein, Albright, and Wells (1945), and Case 6 in Reifenstein and Albright (1947)).

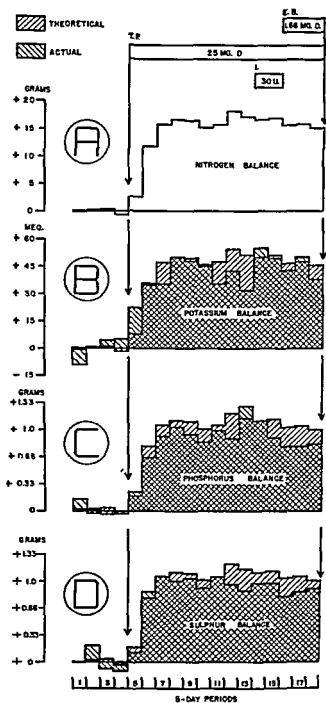


Fig 156

phosphorus were retained, 14.2 gm could be accounted for by the calcium retention, and 18.1 gm by the nitrogen retention. Thus, of the 29.1 gm of phosphorus retained, 32.3 gm were explained by both the calcium and the nitrogen retentions. These figures were obtained from the following calculations:

CALCULATIONS

	27 five-day periods
Phosphorus retained	29.1 gm
Calcium retained	31.7 gm
Theoretical phosphorus based on calcium calcium $\times 1/2.23$ [Shohl (1939a)]	14.2 gm
Nitrogen retained	266.4 gm
Theoretical phosphorus based on nitrogen nitrogen $\times 1/14.7$ [Benedict (1915)]	18.1 gm
Theoretical phosphorus based on calcium and nitrogen	32.3 gm

Fig. 156. A Comparison of the Deviations in the Nitrogen, Potassium, Phosphorus, and Sulfur Balances as a Result of Therapy.

The subject of this analysis was a female patient with Cushing's syndrome (B. V., M. G. H. 74372). (See Fig. 82, page 172 and Case No. 14, Metabolic Study No. 7, page 167). The scales for balances in amounts per five day period are given as the ordinates, the scale of five day periods is given as the abscissa. The analysis consists of 18 five day periods. The horizontal line starting at zero on each ordinate is the baseline of that particular balance, balances extending from the baselines toward the tops of the charts are positive, those extending from the baselines toward the bottoms of the charts are negative. The balances are charted as deviations from the average of the control periods rather than as the balances actually measured. T. P. = testosterone propionate, I = insulin, E. B. = estradiol benzoate, D = dosage per day, U = units per day. The data for potassium are based on analyses of urinary excretions alone, the fecal potassium excretion was assumed to be 8 per cent of the potassium intake. The factors for the calculations are given in Table 8.

The chart has four divisions: A—the measured nitrogen balance, B—the measured nitrogen balance with superimposed theoretical nitrogen balance explainable by the measured potassium balance, C—the measured nitrogen balance with superimposed theoretical nitrogen balance explainable by the measured phosphorus balance (after the phosphorus theoretically retained with calcium had been subtracted), and D—the measured nitrogen balance with superimposed theoretical nitrogen balance explainable by the measured sulfur balance. It will be seen that there is a close correspondence between the measured and the theoretical nitrogen balances. This is evidence that testosterone propionate therapy induced a retention of nitrogen, potassium, phosphorus, and sulfur in the proportions that exist in muscle protoplasm.

For further discussion, see text. Additional data on this patient are published elsewhere [Case 37 in Fraser, Forbes, Albright, Sulkowitch, and Reifenstein (1941), Albright (1942-1943), Case 1 in Albright, Parson, and Bloomberg (1941), Reifenstein, Albright, and Wells (1945), and Case 10 in Reifenstein and Albright (1947)].

The small discrepancy between the measured and the theoretical phosphorus balances would be eliminated by a 10 per cent error in the intake of calcium, phosphorus, or nitrogen. This analysis supports the contention that nearly all of the phosphorus retained as a result of testosterone propionate therapy is retained either with bone or with protoplasm. Further illustrations of analyses of the calcium, phosphorus, and nitrogen balances are given in a previous communication [Reifenstein, Albright, and Wells (1945)].

Calculations such as the above have two purposes: (1) to show any gross errors in the data and (2) to emphasize any situation where the measured balances differ from the theoretical balances. To illustrate this second point it was through calculations such as the one that Albright, Bauer, Ropes and Aub (1929) showed that one of the first actions of the parathyroid hormone is to cause a urinary excretion of phosphorus from a source other than bone or protoplasm (see Fig. 7, p. 19), this source most probably is the inorganic phosphorus of body fluids.

III. THEORETICAL POTASSIUM AND SULFUR BALANCES

If the data include measurements of the balances of potassium and sulfur (both constituents of protoplasm), it is possible likewise to derive theoretical nitrogen balances from the balances of each of these minerals to compare with the measured nitrogen balance (*vide infra*). The factors for such calculations are given in Table 8. Of course if one prefers, one may derive from the measured nitrogen balance a theoretical potassium balance and a theoretical sulfur balance to compare with the measured potassium and sulfur balances.

An illustration of theoretical balances involving potassium and sulfur is presented (see Case No. 14, Metabolic Study No. 7, page 167). In Fig. 156 are charted (A) the nitrogen balance resulting from a therapeutic agent (testosterone propionate), (B) the theoretical nitrogen balance based on the potassium balance, (C) the theoretical nitrogen balance based on the phosphorus balance after the latter had been corrected for the calcium balance, and (D) the theoretical nitrogen balance based on the sulfur balance. The close correspondence of the determined nitrogen balance and the three theoretical nitrogen balances is noteworthy. Thus, during the 14 five-day periods in which the patient received testosterone propionate there was a retention of 211.3 gm. of nitrogen, and the theoretical nitrogen balances based on potassium, on phosphorus and on sulfur, respectively were 217.6 gm., 169.6 gm., and 181.3 gm. These figures were obtained from the following calculations.

CALCULATIONS

	<i>14 five-day periods</i>
Nitrogen retained	211.3 gm
Potassium retained	597.5 meq
Theoretical nitrogen based on potassium potassium $\times 1/2.7$ (factor 6 Table 8)	217.6 gm
Phosphorus retained	12.2 gm
Calcium retained	1.48 gm
Theoretical phosphorus based on calcium calcium $\times 1/2.23$ [Shohl (1939a)]	0.66 gm
Phosphorus not accounted for with calcium	11.54 gm
Theoretical nitrogen based on phosphorus not accounted for with calcium	169.6 gm
phosphorus $\times 14.7$ (reciprocal of factor 8 Table 8)	
Sulfur retained	12.5 gm
Theoretical nitrogen based on sulfur	181.3 gm
sulfur $\times 14.5$ (reciprocal of factor 9 Table 8)	

Further illustrations of theoretical balances involving potassium and sulfur are given in a previous communication [Reifenstein, Albright, and Wells (1945)]

IV CHARTING OF METABOLIC DATA

After having tried many different kinds of charts the authors finally selected the one adopted by Bissett (personal communication) as being the most suitable for most types of balance experiments [see Reifenstein, Albright, and Wells (1945)] It includes in the same chart the balance, the intake, and the urinary and fecal excretions

The method of constructing such a chart (see Fig. 157A) is as follows (A) the scale for intake and balance in gm./24 hr. is given as the ordinate, (B) the scale for time (in this case days) is given as the abscissa, (C) the horizontal line at 0 of the ordinate is the base line to which intake and balance refer, (D) the intake is plotted as an area from the base line toward the bottom of the diagram, (E) the excretion is plotted as a hatched area from the bottom (i.e. the intake) toward the top of the diagram. If the excretion does not reach the base line, a white area is left between the excretion line and the base line, this represents a positive balance. If the excretion reaches the base line, the balance is in equilibrium. If the excretion exceeds the base line, a hatched area is left above the base line, this represents a negative balance. The data are plotted in amounts per 24 hours although the measurements are made on pools of excreta covering the metabolic periods the fecal excretions are charted at the bottom, and the urinary excretions above the fecal excretions. Examples are given in Fig. 7, p. 19 and Fig. 74, p. 152. The advantage of this method of charting over the more

conventional one where the intake and excretion are plotted from the same base line is that it allows one to focus on the most important feature of a balance study, namely the balance (cf Fig 157A and B). It will be seen that both methods are equally good in this respect until the intake is changed, this results in the more conventional method in a discontinuity in the balance.

Where the data represent periods greater than one day, it is preferable to reduce the values to the average value per 24 hours in charting. If one is charting several measurements that have constant interrelationships, the scales should be chosen so that the units express these constant relationships. Thus, when metabolic data referring to calcium, phosphorus, and

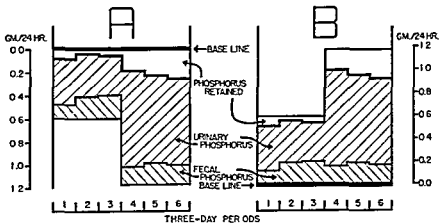


Fig 157 Two Methods of Charting the Same Metabolic Balance Data
(A) Method advocated (B) conventional method where intake is plotted from same baseline as excretions

For discussion see text [From Reifenstein Albright and Wells (1945)]

nitrogen are being charted the units should be chosen so that one unit of the phosphorus scale equals 15 units of the nitrogen scale and two units of the calcium scale (N/P in muscle protoplasm equals about 14.7/1, * Ca/P in bone equals 2.23/1, † for example, see Fig 7, p 19). One objection to this method of charting is that the calcium scale is very small, when the calcium data are important an additional chart with a magnified calcium scale may be desirable (see Fig 103, p 203). Relationships between potassium and nitrogen, and sulfur and nitrogen are treated similarly (for ratios see Table 8, for example, see Fig 156).

The authors wish to stress the importance of including base lines, aver

* [Benedict (1915)]

† [Shohl (1939a)]

age normal levels and zero points for all data that are charted. It is obviously misleading to chart an alteration in the level of a substance unless the column representing the level begins at zero.

V. METHODS OF ANALYSIS AND STUDY

The methods of analysis used in the laboratory are, in general, standard techniques. Urine and stool specimens are analyzed for calcium by the method of Fiske and Logan (1931), phosphorus by the method of Fiske and Subbarow (1925), nitrogen by the Kjeldahl method of Folin (1934) and potassium by the method of Fiske and Litarazek (1934). The sulfur content of the urine is determined by the method of Fiske (1921), the creatine and creatinine content of the urine by the method of Folin (1914) [see also Greenwald and Gross (1924)]. The 17 ketosteroid excretion in the urine is determined by the modification of the Zimmermann reaction (1935) introduced by Callow, Callow, and Limmens (1938), and subsequently further modified by Fraser, Forbes, Albright, Sulkowitch, and Reifenstein (1941). The follicle-stimulating hormone (FSH) excretion in the urine is determined by the method of Klinefelter, Albright, and Griswold (1943). The "11 oxysteroids" (corticosteroids) in the urine are determined by the method of Talbot, Saltzman, Wixom, and Wolfe (1945). The corticosteroid biological activity is assayed by a modification of the Dobriner, Lieberman and Eggleston (1945) adaptation to mice [see also Eggleston, Dobriner, and Rhoads (1944)] of the Remecke and Kendall (1942) test on rats.

The following methods have been employed for serum: calcium, Fiske and Logan (1931), phosphorus, Fiske and Subbarow (1925), alkaline phosphatase, Bodansky (1933), potassium, Fiske and Litarazek (1934), sugar, Folin and Svedberg (1930), chloride, Wilson and Ball (1928), sodium, Butler and Tuthill (1931), protein, Lowry and Hunter (1938) and carbon dioxide, Van Slyke and Neill (1924). The basal metabolic rate is determined by the closed circuit method of Benedict as modified by Roth (1922).

The methods employed in the accumulation, interpretation, and presentation of data pertaining to metabolic balances, notably those of calcium, phosphorus, and nitrogen are discussed in detail elsewhere [Reifenstein, Albright, and Wells (1945)]. A synopsis of other diagnostic procedures can be found in a previous communication [Reifenstein (1941)].

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